
RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

March 7 and 8, 2012

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

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

March 7-8, 2012

The Recombinant DNA Advisory Committee (RAC) was convened for its 128th meeting at 3:30 p.m. on March 7, 2012, at the National Institutes of Health (NIH), Building 31-C, conference room 6, in Bethesda, Maryland. Dr. Yuman Fong (RAC Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 3:30 p.m. until 5:15 p.m. on March 7 and from 8:30 a.m. until 3:15 p.m. on March 8. The following individuals were present for all or part of the March 2012 RAC meeting.

Committee Members

Andrew D. Badley, Mayo Clinic and Foundation (*Day 1 via teleconference, Day 2 in person*)
Michael J. Buchmeier, University of California, Irvine (*via teleconference, Day 2 only*)
Tianxi Cai, Harvard University
Saswati Chatterjee, City of Hope National Medical Center
E. Antonio Chiocca, Ohio State University Medical Center
Rebecca Dresser, Washington University School of Law
Yuman Fong, Memorial Sloan-Kettering Cancer Center (RAC Chair)
Norman Fost, University of Wisconsin–Madison (*Day 1 in person, Day 2 via teleconference*)
Marie-Louise Hammarskjöld, University of Virginia School of Medicine
Joseph A. Kanabrocki, University of Chicago (*via teleconference*)
Hans-Peter Kiem, University of Washington School of Medicine
Walter J. Koch, Thomas Jefferson University
Donald B. Kohn, University of California, Los Angeles
Margaret Mallino, Missoula, Montana
Anna C. Mastroianni, University of Washington School of Law (*Day 1 only*)
David A. Ornelles, Wake Forest University School of Medicine
Susan R. Ross, University of Pennsylvania (*Day 1 via teleconference, Day 2 in person*)
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

Office of Biotechnology Activities (OBA)

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

Ad Hoc Presenters and Speakers

Jeffrey Berns, Hospital of the University of Pennsylvania
Ronald Crystal, Weill Cornell Medical Center
Helen Heslop, Baylor College of Medicine *and* Texas Children's Hospital and the Methodist Hospital
Cliona Rooney, Baylor College of Medicine

Non-Voting Agency Representatives

Kristina C. Borrer, Office for Human Research Protections, U.S. Department of Health and Human Services
Daniel Takefman, U.S. Food and Drug Administration (FDA)

¹ The Recombinant DNA Advisory Committee is advisory to the National Institutes of Health (NIH), and its recommendations should not be considered as final or accepted. The Office of Biotechnology Activities should be consulted for NIH policy on specific issues.

NIH/OD/OBA Staff Members

Linda Gargiulo
Chezelle George
Robert Jambou
Maureen Montgomery
Marina O'Reilly
Gene Rosenthal
Yun Xie

Attendees

There were 64 attendees at this 2-day RAC meeting.

Attachments

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

I. Call to Order and Opening Remarks

Dr. Fong, RAC Chair, called the meeting to order at 3:30 p.m. on March 7, 2012. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* was published in the *Federal Register* on February 14, 2012 (77 FR 8270). Issues addressed by the RAC at this meeting included a report from the Gene Transfer Safety Assessment Board (GTSAB, a subcommittee of the RAC), public review and discussion of three gene transfer protocols, updates and discussion of two clinical trials previously reviewed by the RAC, and discussion of institutional biosafety committee (IBC) review of low-risk human gene transfer protocols.

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. Review and Discussion of Human Gene Transfer Protocol #1201-1144 titled: **AAV8-Mediated Low Density Lipoprotein Receptor Gene Replacement in Subjects with Homozygous Familial Hypercholesterolemia**

Principal Investigator: Patrick Moriarty, M.D., The University of Kansas Medical Center
Sponsor: Daniel J. Rader, M.D., University of Pennsylvania
RAC Reviewers: Dr. Chatterjee, Dr. Kiem, and Professor Mastroianni

Dr. Ross was recused from discussion of this protocol due to a conflict of interest.

A. Protocol Summary

Familial hypercholesterolemia (FH) is a severe genetic disease caused by mutations in the gene encoding the LDL receptor (LDLR). Patients who inherit two abnormal versions of this gene (homozygous patients [hoFH]) have serum cholesterol levels that range from 500 to 1,000 mg/dL and, as a result, develop severe atherosclerosis and lethal heart attacks in childhood.

A few patients have been treated effectively by receiving a liver transplant that results in normal liver expression of LDLR. The proposed clinical protocol aims to deliver normal LDLR genes to the liver cells of research participants by infusing a vector based on an adeno-associated virus (AAV) serotype 8. Studies in mice with the same disease as patients with hoFH demonstrated a reduction in serum cholesterol following infusion of the vector for up to 1 year, which was associated with a regression of atherosclerosis in the animals' arteries. Evaluation of the vector in mice and monkeys confirmed its safety.

This proposed clinical trial will enroll adults with hoFH into three cohorts, with each cohort receiving a different vector escalated one-half log between cohorts. The research participants will receive an intravenous injection of vector and will be monitored for toxicity and evidence of metabolic efficacy by following serum LDL and performing LDL turnover studies before and after gene transfer.

B. Written Reviews by RAC Members

Eleven RAC members voted for in-depth review and public discussion of the protocol. Key issues included the novel approach to gene transfer for hoFH. Although the vector, transgene, and disease application have been involved separately in previous gene transfer research, the combination proposed is novel. In addition, a research participant population with a chronic disease for which other therapeutic options exist and the possible future use of this approach in a pediatric population deserve further discussion.

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

Dr. Chatterjee noted that the paucity of risk-free, effective therapies for this often-fatal disease justifies the proposed study, and that mouse and nonhuman primate models of the disease are impressive and highly encouraging for safety and efficacy, even though these models are not perfectly reflective of the human disease. She also stated that the choice of AAV8 is well justified based on its efficiency in the liver and proven safety and efficacy to date in a hemophilia B trial. Based on the results of the previous AAV8-based hemophilia B trial, Dr. Chatterjee expressed concern regarding possible immune responses at the higher doses proposed for this trial, given the likelihood of research participants' anti-capsid T-cell immune responses. Even though continued transgene expression has been documented despite anti-capsid T-cell responses in several trials, it may be reasonable to avoid them. Research participants will be tested for neutralizing antibodies to AAV8 but the presence of these antibodies is not listed as an exclusion criterion, even though the data from nonhuman primates suggest that transduction may be significantly reduced in these individuals. Dr. Chatterjee queried how the investigators plan to deal with research participants who are tested for T-cell responses to AAV and are found to have baseline anti-AAV T cells. She asked whether human leukocyte antigen (HLA) data would be collected from all enrolled participants, noting that this information could help identify major histocompatibility complex (MHC) elements associated with efficient capsid antigen presentation and could explain person-to-person variability in the intensity and timing of T-cell responses to AAV8 capsids. Dr. Chatterjee asked the investigators to state whether cholesterol-lowering medication would be restarted if sufficient efficacy in this protocol is not observed.

Noting that this protocol is well written and well designed, Dr. Kiem asked the investigators to provide a detailed description of potential side effects with the AAV8 vector. He requested clarification as to how often and for how long the research participants will be monitored for humoral and cellular immune responses and, if immune responses occur, whether the investigators will administer immunosuppressive treatment. The investigators list cancer as a potential side effect and indicate that the vector could integrate, but Dr. Kiem asked how the investigators plan to monitor participants for these risks. He asked how often participants' cholesterol levels would be monitored during the time they are off the cholesterol-lowering treatment, and whether there is a cholesterol reading beyond which the investigators would require intervention. Dr. Kiem also requested that the investigators clarify the risks for participants who go off cholesterol-lowering drugs.

To enhance clarity and understanding for research participants, Ms. Mastroianni suggested rewording in the informed consent document as follows:

- Where the terms “Phase I” and “Phase II” are used in reference to the phases within this Phase I trial, she suggested replacing those terms with “Screening Phase” and “Vector Infusion Phase.”
- On page 1 of the informed consent documents, the definition of gene transfer should be reworded for enhanced understanding and to better communicate the experimental nature of gene transfer.
- Alcoholic beverage intake and avoidance of certain medications should be clarified and listed not only in the protocol but in the informed consent documents.
- The purpose and timing of genetic testing should be clarified, and the disposition and retention plans for the sample and its derivatives should be explained.
- The informed consent documents should include information about payment for transportation from home to Kansas City as well as housing and food during participants’ stay.

Ms. Mastroianni asked whether potential participants who are rejected due to screening would be advised to consult with their personal physician where appropriate and whether they would be given a copy of lab results. She queried whether the investigators or their funding sources intend to protect under patent or trade secret laws either the products or the procedures developed in this proposed study.

C. RAC Discussion

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

- Dr. Kiem asked what the investigators would do if a research participant experiences a cardiovascular event during the four months they are not receiving apheresis.
- Ms. Mastroianni noted that this protocol proposes two informed consent documents that distinguish between the screening process and the vector infusion process. She asked the investigators to clarify what kind of communication will occur with potential participants regarding the vector infusion process to ensure an understanding of the required time commitment.
- Dr. Fong asked about the risk of stopping the apheresis. He inquired whether these participants, more than 17 percent of whom will have had a coronary event, would be monitored routinely and whether they would carry a different risk level for the four months off apheresis.
- Dr. Fong asked whether the livers of these potential participants are inflamed or whether steatosis is present.
- Dr. Fong suggested the investigators include an explicit statement (a guideline rather than a standard operating procedure) about at what level they will treat transaminitis with immunosuppression.

D. Investigator Response

1. Written Responses to RAC Reviews

The types of immune responses that could occur in this trial are T cells to the capsid and transgene and antibodies to the capsid and transgene product. Antibodies to the capsid should have no direct effect on the safety or efficacy of this trial. It is possible that formation of these antibodies could diminish the efficacy of a second dose of AAV8 vector, which is an issue noted in the informed consent document. The other adaptive immune responses that could diminish efficacy and cause transient toxicity would manifest primarily as transient, asymptomatic transaminitis. Little precedent exists for any of these alleged pathogenic adaptive responses except for the example of capsid-specific T cells targeting transduced hepatocytes. The hemophilia B trial, which also used AAV8, noted transient transaminitis concurrent with capsid T cells in at least one participant receiving the highest dose of vector. When comparing total capsid exposure, the highest dose planned for this proposed trial is equivalent to the intermediate dose used in the hemophilia trial; therefore, the reported adverse event is less likely to occur in this proposed trial because no toxicity was observed with the mid-dose used in the hemophilia trial. If toxicity such as hepatitis does occur, the investigators will treat the affected participant using best clinical practices

The investigators plan to include careful evaluation of participants for evidence of cellular immunity to both the transgene product and the capsid, using antigen-specific T-cell assays from peripheral blood mononuclear cells (PBMCs). The appearance of T cells to capsid proteins did not always correlate with toxicity and loss of transgene expression in the hemophilia trial and in a number of other human *in vivo* AAV gene transfer studies. The investigators believe that particles composed of foreign proteins are expected to elicit T cells; however, this kind of response is usually dominated by CD4 rather than CD8 T cells. It is less clear whether these T cells have any pathogenic consequences in terms of toxicity to the target tissue. However, the investigators will presume the capsid T-cell hypothesis is correct and will do whatever is possible to ameliorate it. In terms of capsid load, the highest dose of vector in this trial is equivalent to the middle dose of vector used in the hemophilia study, despite administering 50 percent higher genome-copy doses in each cohort. Review of the T-cell data from the hemophilia study does not indicate ELISpot results above the limit of sensitivity at baseline for any research participants.

Humoral and cellular immune responses will be monitored, and the timeline is indicated in Table 6, Schedule of Events in the Protocol.

The investigators explained that they plan to save PBMCs from the phlebotomies taken for the T-cell studies in case it is necessary to perform repeat enzyme-linked immunospots (ELISpots) or more sophisticated analyses such as intracellular cytokine studies. If toxicity occurs that is ascribed to pathogenic capsid or transgene product-specific T cells, some of the remaining material will be used to characterize HLA haplotypes, a use that is contemplated and permissible under the current informed consent document.

Potential participants with neutralizing antibody titer to AAV8 above 1:10 will be excluded from this study, as noted in the protocol in the inclusion criteria.

The implications of preexisting T cells to capsid are sufficiently unclear to consider using them in formal inclusion/exclusion criteria. Participants will be monitored for liver toxicity as well as T cells to capsid and the transgene product and, if toxicity occurs, the investigators will treat the participant using best medical judgment.

Although the potential for integration of AAV vectors is low compared to retroviral or lentiviral vectors, AAV vector integration events have been reported in animal models. Vector integration into the host chromosome carries with it the potential for malignant transformation, due to gene disruption or activation. The relationship between AAV and cancer is controversial. Latent AAV genomes are widely distributed throughout human tissues, including liver, without any known association with cancer. While two AAV vector mouse studies have detected tumor development, a number of other studies with AAV vectors in animals failed to show an association with cancer. Insertional mutagenesis resulting in leukemia has been reported in several clinical trials employing gamma retrovirus modified hematopoietic stem cells; however, no similar observations have been reported in clinical trials using various AAV serotype vectors expressing multiple different transgenes over more than 12 years of development. The investigators thought it important to disclose the possibility of cancer in the informed consent document and plan to include questions about the incidence of cancer as part of the five year follow-up that will monitor for delayed adverse events related to the gene transfer.

The protocol calls for participants to be withdrawn from cholesterol-lowering therapy one month prior to vector administration and to remain off therapy for three months after vector administration. Because hoFH patients have poor response to cholesterol-lowering medication, withdrawal of oral therapy is not expected to result in substantial increases in cholesterol levels. The investigators do not plan to re-initiate cholesterol-lowering therapy prior to three months post administration. At that point, the default will be to re-initiate previous cholesterol-lowering therapy in all research participants. In the event that a research participant's cholesterol level has been reduced to a point at which re-initiation of cholesterol-lowering therapy may not be necessary, it will be up to the discretion of that individual's clinical lipidologist as to whether to re-initiate therapy.

The investigators will measure cholesterol levels frequently within the first three months (at days 3, 4, 7, 14, 30, and 60, and at month three post vector administration). However, the investigators explained that no upper threshold would result in re-initiation of cholesterol-lowering therapy sooner than the three month time period. The risk associated with being off cholesterol therapy for four months is considered small for three reasons: 1) The effects of cholesterol-lowering therapies in hoFH patients is modest at best; 2) The timeframe is relatively short in the context of atherosclerotic disease development; and 3) No acute risk is associated with elevated LDL cholesterol levels.

As to whether genetic testing will be conducted before and after vector administration, the investigators clarified that blood will be drawn at the screening visit only for genetic sequencing of all LDLR exons to determine mutations that may be causal for hoFH. Future genotyping will not be done after vector infusion since the genotype will not have changed. The samples will only be used in this study.

The investigators agreed to add a table of study visits and procedures to page 8 of the vector infusion informed consent document.

The investigators stated that they do not anticipate any new intellectual property emerging from this proposed clinical study. If new discoveries are made, they intend to publish the data associated with the discoveries along with the clinical results when deemed appropriate by the research team.

The investigators agreed to implement wording changes in the informed consent document so as to make the language accurate and more understandable, to characterize how blood samples would be used, and to avoid the therapeutic misconception.

2. Responses to RAC Discussion Questions

If they encounter reactivity to AAV8 capsids, the investigators do not plan to treat preemptively with transient immunosuppression, in large part because they do not know what it means to have preexisting T cells to capsid, in terms of toxicity or efficacy of transduction. However, for a participant who has been dosed, the investigators might consider administering immunosuppression (e.g., a short course of prednisone) if appropriate.

Regarding cancer as a potential side effect, Dr. Rader acknowledged that cancer is a theoretical risk associated with AAV vectors. The investigators will monitor clinically for cancer and record whatever cancer develops, but they are not proposing to conduct scans to look actively for cancer; they are proposing a reactive approach to this theoretical risk.

The investigators explained that, in the event a participant had little response to the gene transfer and was in the middle of their four month study period and had a heart attack, they would reassess whether to put that individual back on LDL apheresis. Although doing so would be a protocol deviation, it would be clinically necessary if the person's lipids were extremely high and a strong correlation existed between the high lipid reading and the cardiovascular event. The decision to do so would be made on a case-by-case basis.

Dr. Rader explained that the consent process, which will be carried out by the core team, will involve a description of the overall protocol and project in general terms. The time commitments involved and some general aspects of the safety issues will be emphasized as key aspects. The investigators intend the process to provide enough information to potential participants so that they have a sense of the time commitment and safety issues if they are eligible and if they decide to participate in the infusion protocol.

Dr. Rader stated that neither Dr. Moriarty nor he have any financial interest in the outcome of this clinical trial.

Regarding the risk of stopping the apheresis, Dr. Rader explained that clinical management is different for these individuals, and the value of stress testing is unclear. A clear positive stress test would be followed by angiography. If significant stenosis is found and with the likelihood of an intervention within six months,

that individual would not be eligible to participate in this trial. If significant lesions are found but the individual has been stable for six months, that person would be eligible to participate.

With regard to the status of the livers of potential participants, Dr. Rader explained that data generated during recent years using noninvasive methodology to look at hepatic fat in patients with hoFH concluded that these individuals do not have fatty livers; most appear to have less fat than average in the liver even though they have high amounts of LDL in the blood and they do not tend to have liver function test abnormalities. No evidence exists that hoFH patients have any kind of preexisting hepatotoxicity.

Dr. Rader agreed to discuss again with the investigator team about including an explicit statement about the point at which treatment with immunosuppression would be considered.

E. Public Comment

No public comments were offered.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

Clinical and Trial Design Issues

- HLA typing of participants should be included in the protocol. A retrospective correlation between MHC haplotypes and T-cell responses to AAV8 capsids may allow for the identification of MHC elements associated with efficient capsid antigen presentation and help explain individual variability in the intensity and timing of T-cell responses.
- The protocol should include criteria to guide when immunosuppression will be administered in the event of an unexpected increase in liver blood tests that may indicate a T-cell response against transduced liver cells. The protocol should also include immunosuppressive regimens but can be written to still allow for individualized clinical care.

Ethical, Social, and Legal Issues

- Participants will sign an informed consent document that will allow them to be screened and another informed consent document if they meet the eligibility criteria to enter the trial. The screening informed consent document should include additional information describing the trial, including the expected time commitment, the necessity of forgoing cholesterol-lowering therapy for 4 months, and the issues related to safety for this protocol. Inclusion of this information is particularly important, as potential participants will not necessarily be screened at the main trial site.
- The section of the informed consent document that discusses the risks of withdrawing cholesterol-lowering therapy 1 month prior to vector administration should include further discussion regarding the ongoing monitoring of the research participants' cholesterol levels and that their clinical care will remain the priority throughout the trial.

G. Committee Motion 1

Dr. Fong summarized the RAC recommendations to be included in the letter to the investigators, expressing the comments and concerns of the RAC. Dr. Chatterjee moved and Dr. Yankaskas seconded that these comments be approved by the RAC. The RAC voted to approve these summarized recommendations by a vote of 16 in favor, 0 opposed, 1 abstention, and 1 recusal.

III. Minutes of the December 13–14, 2011, RAC Meeting

RAC Reviewers: Drs. Badley and Ross

Dr. Ross stated that the minutes document was satisfactory and proposed that this document be entered into the record. Although no motion was made and no vote was taken, no objections were noted.

IV. Gene Transfer Safety Assessment Board Report

RAC Reviewers: Drs. Badley, Chiocca, Fong, Kohn, Strome, and Yankaskas

A. GTSAB Report

Dr. Yankaskas reported that OBA had received 12 protocol submissions in the past three months, nine of which were not selected for public review at this RAC meeting. Of the nine protocols not selected for public review, seven were oncology protocols and one each was for hemophilia and heart failure. In these nine protocols, three used plasmid vectors, two each used adenovirus vectors and retrovirus vectors, and one each used AAV and transposon vectors.

Fifteen serious adverse events (SAEs) from nine protocols were reviewed by the GTSAB, including initial and follow-up reports. After analysis of these events, the GTSAB concluded that none warranted public discussion at this RAC meeting.

The OBA received notification from investigators that 17 protocols were newly open to enrollment. Five of those 17 had previously been reviewed at a RAC public meeting. The GTSAB highlighted the key elements of those five protocols:

- *OBA Protocol #878, reviewed by the RAC in December 2007: A Pilot Feasibility Study of Oral 5-Fluorocytosine and Genetically Modified Neural Stem Cells Expressing E. Coli Cytosine Deaminase for the Treatment of Recurrent High-Grade Gliomas.* Preclinical studies were conducted on a model with prior radiation to assess whether radiation could alter the tumor environment and make the neural stem cells, which had been transformed with a *c-myc* oncogene, prone to produce tumors. The effect of radiation on the ability of the cells to migrate to the tumor was also evaluated. Radiation did not change the safety profile of the cells in these models. Animal and cell migration studies also determined that dexamethasone did not alter either the tumorigenicity or the tropism of the stem cells. Dexamethasone is commonly prescribed in patients with gliomas.
- *OBA Protocol #989, reviewed by the RAC in September 2009: A Phase 1 Open Label Escalating Dose Study of the Safety and Tolerability of Single Daily Doses of CEQ508, an RNAI-Based Therapy for Familial Adenomatous Polyposis.* The response notes that immune responses to listeriolysin O, one of the bacterial compounds of the study agent (CEQ508), have not been seen in preclinical studies or in a previous Phase I trial. The mutation seen in this disease leads to increased β -catenin, which leads to upregulation of genes involved in cell proliferation, including the *c-myc* oncogene. Additional analysis of correlations among oncogenes, β -catenin, and clinical outcomes is being considered. Only individuals with a documented mutation in the adenomatous polyposis coli gene or a clinical diagnosis and a family history of this autosomal dominant disease will be enrolled in this study.
- *OBA Protocol #1024, reviewed by the RAC in March 2010: Lymphodepletion Plus Adoptive Cell Transfer with CXCR2 and NGFR Transduced T Cells Followed by High-Dose Interleukin-2 in Patients with Metastatic Melanoma.* This study will employ a Bayesian approach to the Phase I dose escalation so that dosing cohorts will be informed by the ability of a prior cohort to tolerate the transduced tumor infiltrating lymphocytes (TILs), which may expand significantly *in vivo* or be eliminated rapidly. Given recent data that the CD4+ T cells may be critical to antitumor activity, in addition to examining the tumor site for the presence of CXCR2-transduced TILs, the investigators will examine whether CD4+ T cells are present. The age limit for pediatric participants has been clarified to age seven and older, rather than relying on intellectual age.

- *OBA Protocol #1049, reviewed by the RAC in September 2010: A Phase I/Phase II Open Label Single Center Multiple Dose, Dose Escalation Study To Evaluate the Safety and Tolerability of SNSO1T Administered by Intravenous Infusion in Patients with Relapsed or Refractory Multiple Myeloma.* SNSO1T is a nanoparticle plasmid complex containing a gene for translation initiation factor 5A (eIF5A) protein and a silencing RNA (siRNA) against the same native eIF5A. In myeloma cells, the eIF5A is hypusinated, which promotes cell growth and is the target of the siRNA. Unhypusinated eIF5A that will be made by the plasmid should then promote apoptosis. Preclinical models reviewed at the RAC meeting employed subcutaneous injection. However, results of toxicology studies demonstrate that intravenous administration leads to plasmid DNA in the bone marrow. The clinical trial will examine bone marrow samples to determine whether apoptosis is occurring in myeloma cells. During RAC review, concern was raised regarding whether the study agent could alter the expression of the eukaryotic translation initiation factor 5A-like 1 (eIF5AL1). Data was presented that eIF5AL1 appears to be a pseudogene and is not expressed in a myeloma cell line. Given the sequence homology between eIF5AL1 and eIF5A, any expression would likely be silenced by the siRNA.
- *OBA Protocol #1101, Reviewed By The RAC In June 2011: A Randomized Double-Blind Phase III Efficacy Trial of PROSTVAC ν GM-CSF in Men with Asymptomatic or Minimally Symptomatic Metastatic, Castrate-Resistant Prostate Cancer.* Additional information was added to the protocol that articulated the rationale for using an empty fowl pox vector rather than a vaccinia virus vector (the backbone of the study agent) as the placebo control. Detailed instructions and precautions will be provided to those individuals who will prepare the study agent for injection or who will interact with participants to ensure that the vector is handled in a safe manner and that healthcare workers are informed of the potential risks.

B. RAC Discussion

No discussion occurred.

C. Public Comment

No public comments were offered.

V. Day 1 Adjournment

Dr. Fong, RAC Chair, adjourned Day 1 of the March 2012 RAC meeting at 5:15 p.m. on March 7, 2012.

VI. Day 2 Call to Order and Opening Remarks

Dr. Fong, RAC Chair, called to order Day 2 of the March 2012 RAC meeting at 8:30 a.m. on March 8, 2012.

VII. Discussion of Results from Protocol #977 titled: 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

Presenter: Ronald Crystal, M.D., Weill Cornell Medical College, New York Presbyterian Hospital

A. Presentation

Dr. Crystal presented an update of the results from this protocol. Late infantile neuronal ceroid lipofuscinosis (LINCL) is an autosomal recessive disease occurring in 400 and 600 individuals worldwide.

Disease onset occurs between the ages of two and four years, and manifests as cognitive impairment, visual failure, seizures, and deteriorating motor development, leading to a vegetative state and death by age 12. LINCL is caused by mutations in the CLN2 gene. This gene codes for tripeptidyl peptidase, a proteolytic enzyme. Deficiency of the enzyme leads to accumulation of lipopigments in the lysosomes causing the neurons to die over several years. Dr. Crystal explained the two ongoing protocols for this disease—the NIH protocol, which has a control arm, and a parallel foundation-funded protocol, which is being conducted to obtain more safety information from other genotypes and more severely affected children.

LINCL offers some advantages for gene transfer. One important general lesson learned in gene transfer is that the transferred gene cannot be inserted into every cell. Tripeptidyl peptidase is secreted as a precursor, which is then taken up in surrounding cells through the mannose-6 phosphate (M6P) receptor. The hope is that getting the gene into a significant number of cells will result in cross-correction of other cells in the local area.

Dr. Crystal summarized the toxicology information from the nonhuman primate studies. Before starting the two clinical studies, the investigators noticed that some inflammation persisted in the nonhuman primates three months after dosing. Because this inflammation did not have clinical sequelae, they decided this meant that the dose was just below the toxicity level and they proceeded with the two clinical trials.

The outcome measures for the NIH trial are a clinical score on the Weill Cornell LINCL Scale and quantitative MRI; secondary measures varied and were not useful. In their NIH trial, the investigators have screened 26 children and have dosed four males and three females, from 3.5 years old to 7 years old. Six of those children have been evaluated at six months post dosing and two of them at 12 months post dosing. In the parallel protocol, the investigators have dosed one male and two females, ages 5 years, 11 months, to 8 years, 4 months. The first participant was withdrawn before the 6-month follow-up visit and the second participant will reach the 6-month visit in April 2012.

The primary reason for Dr. Crystal's presentation was to share what the investigators have observed in the MRI imaging—a localized MRI abnormality at the site of vector administration that does not appear to result in clinical sequelae. A T2/FLAIR with diffusion restriction was evident post-operatively at Day 1 but persisted at the 6-month follow-up MRI in four of the six children who had reached that point; in two of those six children, this abnormality was present at Day 1 but disappeared at 6 months. In addition, the investigators saw this abnormality again at 12-month follow-up for two of the four children who were positive at 6 months. The investigators have evaluated quantitatively a variety of MRI parameters, including diffusion coefficient, T2 values, parent diffusion coefficient of water, fractional anisotropy, percent cerebral spinal fluid volume, and spectroscopic analysis. These MRI parameters show no difference between the children that have the abnormality and those who do not.

The investigators have discussed with their data with the safety monitoring board (DSMB) and the FDA regarding what to do about the appearance of this abnormality. Although some concern was expressed by the FDA that lowering the dose might result in loss of efficacy, the investigators proposed and the DSMB and FDA agreed that the dose would be lowered by one-half log. This lower dose has been administered to three children to date, one in the parallel protocol and two in the NIH protocol; none has yet reached the 6-month follow-up point.

B. RAC Discussion

Dr. Badley asked the investigators whether they have done any measurements to look at preexisting immunity to AAV10 proteins and whether or not that correlates with the MRI findings. Dr. Crystal explained that they have looked for humoral immunity and cellular immunity. The investigators have seen no cellular immunity either to the capsid or to the transgene. In regards to humoral immunity, one of the children had a small predosing cross-immunity to this nonhuman primate capsid, but this individual was not one of the children who showed the abnormality.

Dr. Yankaskas asked about the average number of sites with signaling. Dr. Crystal responded that the investigators have not seen this abnormality at all of the 12 imaged sites in each participant. Looking at all the MRI slices, the abnormality is visible in 50 percent to 60 percent of the sites, and the investigators assume the abnormality is present but not visible in the other sites.

Dr. Fong inquired whether the investigators have seen anything in the nonhuman primate brains that looks like this abnormality. Dr. Crystal explained that the investigators do not have MRI data on the nonhuman primates. However, they have looked at the histology and have found mild inflammation in the area around the site of vector administration. Given that information, the investigators believe that the abnormality in the children likely is inflammation and edema in that local area, which disappears as it spreads out.

Dr. Chiocca wondered whether the investigators were certain that the abnormalities were located at the injection sites. Dr. Crystal explained that the abnormalities track precisely with the injection sites.

Dr. Fong suggested considering more injection sites with a lower dose at each site, and asked whether the investigators have data to indicate whether that approach should be contemplated. Dr. Crystal stated that the investigators have no data about this approach. Their initial decision to use 12 sites was based on the desire to limit the anesthesia time so as to limit adverse events associated with anesthesia. New funding for leukodystrophy research from the National Institute of Neurological Disorders and Stroke is allowing the investigators to compare multiple different administration strategies; they are comparing intraventricular administration, different catheters, and other strategies for ramping up the diffusion volumes. These strategies are under investigation and data will be available eventually, but Dr. Crystal averred that the process used in this LINCL trial is the best available at present.

C. Public Comment

No public comments were offered.

[Dr. Fong recused himself from chairing the next two sections of this RAC meeting due to conflicts of interest. Dr. Kohn was appointed interim RAC chair during Dr. Fong's absence.]

VIII. Review and Discussion of Human Gene Transfer Protocol #1201-1145 titled: Phase I Study of Direct Administration of AdVEGF-All6A+, a Replication Deficient Adenovirus Vector Expressing a cDNA/Genomic Hybrid of Human Vascular Endothelial Growth Factor to the Ischemic Myocardium of Individuals with Diffuse Coronary Artery Disease via Minimally Invasive Surgery

Principal Investigators:	Todd Rosengart, M.D., Stony Brook University Medical Center and Weill Cornell Medical College; Ronald Crystal, M.D., Weill Cornell Medical College, New York Presbyterian Hospital
Sponsor:	Ronald Crystal, M.D., Weill Cornell Medical College, New York Presbyterian Hospital
RAC Reviewers:	Ms. Dresser, Dr. Koch, and Dr. Ornelles

Dr. Fong was recused from discussion of this protocol due to a conflict of interest.

A. Protocol Summary

Diffuse coronary artery disease (CAD) causes widespread damage in the coronary arteries that supply blood, nutrients, and oxygen to the heart. CAD is the leading cause of death for men and women in the United States. This two-part, multi-center, placebo controlled research study aims to: (1) determine the safety/toxicity of direct administration of the vector AdVEGF-All6A+ to the ischemic myocardium to individuals with diffuse coronary artery disease for which there is no other therapy; and (2) to generate

preliminary evidence regarding whether direct administration of AdVEGF-All6A+ to the ischemic myocardium will induce growth of collateral blood vessels and improve cardiac function in this same population.

This study is proposed to take place in two parts. Part A will examine the safety of a gene transfer vector, AdVEGF-All6A+, delivered directly to the heart of individuals with diffuse CAD. Three different doses of the drug will be tested in a total of nine individuals. The first three research participants will receive 1×10^7 particle units (pu) of the drug, the next three participants will receive 1×10^8 pu, and the final three participants will receive 1×10^9 pu, via minimally invasive surgery. Participants in Part A will be followed for three months post surgery and then annually for 15 years.

Part B aims to gain additional safety data and to develop preliminary efficacy data to determine whether administration of AdVEGF-All6A+ to the heart will lead to the growth of collateral blood vessels and improve cardiac function in individuals with diffuse CAD. Part B will enroll 32 participants, who will be assigned randomly to one of two study arms. Twenty-four participants will undergo surgery and receive the maximum tolerated dose of AdVEGF-All6A+ as determined in Part A. Eight participants will undergo surgery but receive the AdNull placebo gene transfer vector, which is the same vector as AdVEGF-All6A+ but without the therapeutic gene. Neither the participant nor the physician will know which vector is being administered. Participants enrolled in Part B will be followed for six months post vector administration.

The primary endpoint is time to 1 mm ST segment depression during standard exercise. In the absence of a 1 mm depression, time to termination of exercise tolerance test will be used. Secondary endpoints include stress echocardiogram, assessment of angina, and computed tomography coronary angiogram.

B. Written Reviews by RAC Members

Eight RAC members voted for in-depth review and public discussion of the protocol. Key issues included that it is the first cardiac protocol to use a vector as a placebo and the first protocol to use a vector in a placebo arm this early in protocol development. The adenoviral vector proposed for this protocol contains a gene (E4orf1) that can have an impact on endothelial cell survival and proliferation; therefore, the risks and benefits of employing this placebo in this trial at this stage was deemed to deserve further discussion.

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

Dr. Dresser inquired as to the expected lifespan and quality of life for the research participant population and asked why the investigators believe the risks to these individuals as well as the risks to the placebo group (who will undergo surgery but will have no chance of direct benefit) are acceptable. She requested that the investigators discuss how the research team plans to address the various challenges of enrolling trial participants from Doha, Qatar, one of the proposed study sites. With regard to the informed consent document, Dr. Dresser suggested that some medical and scientific language is expressed in terms that are too complex for a layperson and that an eighth-grade reading level should be used, the consent form should ensure that potential participants understand that harm is a possibility and that a low chance of direct benefit exists, and the material on compensation for research-related injury is confusing and should be clarified.

The primary concern expressed by Dr. Koch was the lack of preclinical data with this new vector in a pig model of cardiac ischemia, especially because that data is essential to determining a solid rationale for adding a new Phase I trial in light of VEGF121 results. He suggested using a catheter-based approach using the NOGA Cardiac Navigation System to guide direct injection into ischemic areas from the left ventricle, an approach that might be safer and more precise and that could be tested and perfected using a pig model. Dr. Koch asked the investigators to explain their rationale for proposing to use this vector as opposed to conducting a Phase III or larger study with VEGF121, which has been shown to be safe in early trials. He asked why a vascular endothelial growth factor (VEGF) ELISA is not part of the follow-up as a measure of gene delivery, why steroids and immunosuppressants are exclusion criteria, and whether the investigators should consider including lessening of angina or angina symptoms as a primary objective of this proposed study. With regard to the informed consent document, Dr. Koch asked the

investigators to include a description of VEGF121. He noted that the Appendix references a rat model of myocardial infarction but that no data was included; in addition to providing the rat data, Dr. Koch reiterated the appropriateness of a pig ischemic model that could be used to determine the percent of cells transduced by the virus. Dr. Koch also suggested that a VEGF ELISA after gene delivery in research participants could be helpful in determining gene expression; with three doses, a dose response could be identified, which would add confidence to viable expression.

Dr. Ornelles identified no major concerns regarding the safety of the vector or the experimental design. However, he noted that the unusual nature of the synthetic transgene introduced in this vector leads to concerns about the possibility that unexpected splicing events could result in expression of adenovirus open reading frames from this novel vector, and that unexpected outcomes could arise during the proposed trial; he requested comment from the investigators as to whether this possibility had been evaluated during the studies performed with heart models from the dog or pig. He asked whether the triple VEGF vector could introduce toxicities that warranted inclusion of a null adenovirus vector as a control, and whether adverse effects not seen in animal models might arise in humans. Because of the increased mortality in tumor-bearing rats following administration of the AdVEGF-All6A+ and its ability to promote tumor growth compared to the AdVEGF-All6A+ vector, Dr. Ornelles wondered whether a similar phenomenon could occur in the heart and whether the efficacy observed in the larger animal models could be expected to be similar to the efficacy likely to be observed in humans. With regard to the informed consent document, Dr. Ornelles suggested that the language may be too technical, although he noted the value of the clarity and completeness of the information provided. Dr. Ornelles also noted several specific points in parts A and B of the informed consent document that required revising for clarity or accuracy.

C. RAC Discussion

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

- Noting the small control group, Dr. Cai asked the investigators whether they were concerned about their ability to capture efficacy.
- Dr. Strome requested that the investigators consider informing potential participants that a plant-based-only diet may reverse their CAD.
- Dr. Strome expressed concern about the informed consent process for the participant population in Qatar.
- Dr. Kiem requested clarification about which patient populations the investigators are targeting, and whether those individuals will or will not be able to get a stent or bypass operation.
- Dr. Kohn asked whether vascular formation, encouraged by the virus, will persist long term.
- Dr. Kohn brought up the importance of conducting interim analyses if efficacy is shown, so the placebo arm can be stopped. He also asked about the stopping rules for this proposed trial.

D. Investigator Response

1. Written Responses to RAC Reviews

All participants are individuals with coronary artery disease that significantly affects everyday living, and they have no other therapeutic options. This group is at a significant risk for death, and the five-year survival estimate for individuals with class III or IV angina on the Canadian Cardiovascular Society scale is 52 percent. Participants will have no isolated coronary artery lesions, will no longer have the option of coronary artery bypass surgery or coronary artery stenting, and will already be on optimal medical therapy (which will be continued). While risks exist for the individuals participating in this study, based on their prior experience the investigators believe these risks are acceptable because these individuals have disabling diffuse CAD a fatal disorder with no other therapeutic options, and are adults who can make an informed decision as to their participation based on the consent process.

The investigators agreed to require participants to write an explicit acknowledgement regarding the possibility of receiving only placebo surgery that would not likely benefit their diffuse CAD. This new

statement has now been included in the signatures section of the informed consent document and participants will be required to initial it.

Regarding the portion of this proposed study that will take place in Qatar, the investigators explained that the protocol will be reviewed by the local ethics committee at Hamad Medical Corporation and by the institutional review board (IRB) at Weill Cornell Medical College–Qatar, which has the same rigor and follows the same regulations as the IRB at Weill Cornell Medical College–New York. The studies currently being performed in Doha, Qatar, are conducted by research coordinators who are fluent in English and Arabic. All participants are consented with consent forms approved by Hamad Medical Corporation and Weill Cornell Medical College–Qatar, which explain the study in both English and Arabic, and the informed consent process is presented in each participant's native language.

At this RAC meeting, the investigators presented data for the AdVEGF-All6A+ vs. AdNull vectors in a rat model with a ligated left coronary artery-induced myocardial infarction and simultaneous administrations of the VEGF-All6A+ or AdNull vectors to the myocardium. The data demonstrates that both vectors are safe in this model under severe myocardial ischemic conditions.

In response to Dr. Koch's suggestion to use a pig model before moving to humans, the investigators stated that carrying out a pig model would take a minimum of 1.5 to 2 years and would be prohibitively costly. While a pig study would be of academic interest, it would add little to what is already known. The human disease is a chronic, complex disease and is not the same as a pig atherosclerotic disease.

Acknowledging that the NOGA Cardiac Navigation System is an interesting idea, the investigators stated that no data exists in humans to show that it works for effective gene transfer, and the data suggests that a substantially reduced area of the target tissue is injected. The mini-thoracotomy approach proposed for this trial is safe and gives absolute control of vector administration. In contrast, the NOGA catheter-based approach cannot guarantee that the dose is actually administered to the myocardium, and an intravascular leak is possible, with a consequent loss of potential efficacy, risk of vector delivery to other organs, and induction of a cytokine storm with consequent serious adverse events or death.

The AdVEGF121 vectors tested in the earlier clinical studies were shown to be safe, but a conclusion regarding efficacy was not possible for the reasons that have led the investigators to include a placebo control arm in their proposed study. In the decade since the AdVEGF121 clinical trial, they have developed a cDNA/genomic hybrid transgene with higher potency and improved safety at a lower dose, which justifies the use of the new gene transfer vector.

Plasma VEGF will be assayed multiple times in this study. In the context of transient adenovirus expression typical of gene transfer studies, the investigators do not expect to see elevated VEGF levels at the end of this study.

Steroids and immunosuppressants are listed as exclusion criteria because they could interfere with the required immune-mediated shutdown of the adenovirus gene transfer vector. The use of those agents also would mask identification of immune/inflammatory adverse effects. The use of these agents for a post-vector administration hyperinflammatory response will be the decision of the treating physician.

The investigators reiterated that the primary endpoint is the quantitative measure of time to 1 mm ST depression during exercise. The more subjective measure of angina, as measured by the Canadian Cardiovascular Society Functional Classification of Angina Pectoris, is a secondary endpoint.

The investigators explained that there is no way to evaluate VEGF in the myocardium of the clinical patients. Knowing the number of transduced cells or the VEGF levels in the myocardium of an animal model is not informative because an effective dose for an artificially induced ischemic or myocardial infarction model cannot be translated to the target diffuse CAD in humans.

The investigators agreed to develop an investigative strategy to look for unexpected spliced products in the myocardium of animals injected with AdVEGF-All6A+ and control vectors, and said they would not initiate the clinical study until this vector and the control vector is proven not to be a safety issue.

No toxicity is expected due to the use of the genomic/cDNA hybrid spliced transgene, based on an extensive safety and toxicology study in 210 rats at three doses in a myocardial infarction model that included the AdVEGF-All6A+ and AdNull vectors, which showed no untoward results. The investigators explained that efficacy is the primary reason for inclusion of a control arm with AdNull. The literature has shown that needle sticks in the heart (without any vector) can evoke angiogenesis, and adenovirus vectors induce local macrophage accumulation and VEGF expression. Without a proper AdNull vector control, assignment of drug efficacy to the VEGF transgene would remain in question and further development of the drug would be limited by this caveat.

Increased risk for tumorigenesis due to angiogenic gene transfer in humans is theoretical only. The issue originally came up secondary to the results of experiments with persistent retroviral-mediated VEGF expression in immune-deficient mice, an experiment specifically designed to release a large dose of soluble VEGF into the circulation with a previously established and aggressive VEGF-dependent tumor. Additional studies, also in immune-deficient mice, with tumor cell lines that were transfected with each of the three VEGF isoforms demonstrated that the VEGF121 isoform has the greatest capacity for tumorigenicity. The investigators noted, therefore, that their new vector, AdVEGF-All6A+, delivered at a significantly lower dose than the original AdVEGF121 vector, encompasses a precautionary approach. The expected safety profile is also improved by the choice of an adenoviral vector that mediates only transient expression of VEGF, and the protein is short lived. There are no proven clinical examples of tumorigenesis from the use of VEGF protein or vectors in humans.

The relative potency of cross-species VEGF function is unknown. The VEGFAll6A+ gene is human derived and might be expected to be equally or more potent in humans than in other species; human VEGF is clearly potent in angiogenic models in many species, from mice to nonhuman primates. The translation of dose response from animals to humans is not predictive and thus the use of dose escalation in Part A of this proposed study, starting at a low dose that is minimal based on previous studies, is designed to guard against the possibility of a potent response in humans.

In the REVASC study [*Gene Therapy* (2006) 13, 1503-1511], significant improvements were observed with more than a 30 percent change in ST depression, even though the study was not designed to be powered for this result. Because of the consistency in the measures of ST depression observed in that study, the investigators believe that their proposed study, which is similar in power to the REVASC study, will allow the detection of significant changes in cardiac function using this parameter.

Adenoviral vectors are generally accepted as transient gene delivery vehicles due to a combination of innate and evoked immune mechanisms. Dilution of the vector by mitotic mechanisms is important in tissues with rapid turnover rates but not in the myocardium. In prior studies conducted by the investigators with AdVEGF121, using higher doses, no problematic cardiac events were observed; in addition, the investigators did not observe any problematic cardiac-related events in their safety and toxicology studies.

Data suggests that some benefit may result from needle stick when as the placebo AdNull is administered, although the VEGF-All6A+ transgene in the AdVEGF-All6A+ vector is the therapeutic agent that drives angiogenesis. Theoretically, some benefit could result from the placebo AdNull vector. Myocardial puncture *per se* can induce an angiogenesis response, likely by inducing a mild (subclinical) transient local inflammation, including the recruitment of macrophages that express VEGF.

Responding to suggestions by the RAC reviewers, the investigators agreed to revise the consent forms for Part A and Part B to be written in lay terms, to include simplified descriptions, and to clarify several terms and processes.

2. Responses to RAC Discussion Questions

Dr. Crystal stated that the investigators have added a patient advocate as part of the consent process. He also explained that the investigators have decided to offer participants who were in the placebo arm the possibility of receiving the active drug.

Regarding the possible difficulty of uncovering efficacy with such a small control group, Dr. Crystal noted that the adenovirus alone and the needle stick alone could confer some positive effects, although the investigators believe those effects will be outweighed by the VEGF effects, which have been proven by prior studies. The investigators have designed this trial to balance the resources, numbers, and safety, hoping to see an efficacy difference between the active and control groups that will suggest further development and testing of this drug in larger clinical trials.

Dr. Crystal agreed to discuss internally with his team about reviewing with potential participants the possible positive aspects of dietary control of their CAD. He also agreed to make sure to include in the informed consent document the full range of studies of CAD treatments, including the use of lasers to make microperforations that would result in revascularization of the affected area.

The investigators plan to conduct the initial, dose-ranging safety study in the United States. Doing so will give them more time to think about how best to provide informed consent to the research participants in Qatar. They are consulting with the ethics and consent experts in Qatar.

Dr. Crystal reiterated that these patients have diffuse CAD and most are diabetic. Most of them will have had a bypass or a stent procedure, and they have no local lesions that can be treated by that methodology. They will also be on maximum medical therapy.

Dr. Crystal acknowledged that the investigators do not know whether the new vascular formation encouraged by the presence of the virus will persist long term. However, the investigators have written a protocol to determine what has happened to research participants they treated with VEGF 10 years ago. Although there was no control group in that trial, a large percent of those individuals are still alive and functioning well, and have not experienced adverse events. The literature indicates that at least half of a population with the characteristics of this participant group will die by year five, so the long-term result from this trial appears significant.

Regarding conducting interim analyses, Dr. Crystal agreed that having multiple reviews at reasonably close intervals will be essential for determining whether to stop the placebo arm if efficacy occurs. Stopping rules for individual participants or for cumulative number of SAEs will be in place, similar to the rules for the investigators' original trial ten years ago.

E. Public Comment

No public comments were offered.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

Preclinical Issues

- The native splicing sequences of the VEGF transgene have been modified by site-directed mutagenesis to promote a higher yield of VEGF189 and lower yields for VEGF121 and VEGF165. The transgene contains modified introns with synthetic splicing signals and this modification could result in unexpected spliced products. The investigators have agreed to address this potential safety issue by examining the myocardium of animals that have been injected with AdVEGF-A116A+ and control vectors for any such aberrant products. This examination of the preclinical data will occur prior to the initiation of this study.

Clinical and Trial Design Issues

- The data and safety monitoring plan should include an interim analysis that will measure whether the active agent has demonstrated statistical efficacy compared with the control arm. There should also be a stopping rule based on this analysis so as to minimize the number of participants who receive empty vector if a clear efficacy signal is seen with the active agent.

Ethical, Social, and Legal Issues

- The decision to use a control group in this early trial is not unreasonable, given the low risk of the surgical procedure and the fact that the administration of an empty adenovirus could have a small positive clinical effect by promoting angiogenesis due to the minor surgical procedure or local reactions to the adenoviral vector. However, it is critical that the informed consent process be rigorous to ensure that participants understand the randomization process and that, if assigned to the control arm, they are highly unlikely to receive any clinical benefit. Clinical benefit is very unusual in any early phase clinical trial, but it is particularly important that participants who will receive the empty adenoviral vector understand that the therapeutic efficacy of the AdNull vector is not being tested. One mechanism is to ask participants to sign a written statement acknowledging that they may receive an adenoviral vector that is not designed to have clinical effect and that the surgical delivery of this adenoviral vector very likely will not provide any clinical benefit.
- If efficacy in the active arm is seen in this trial, those participants enrolled in the control arm may want to receive the active agent. It is important to discuss, during the informed consent process, if and under what circumstances participants who receive the control vector will have the opportunity to receive the active agent. This includes a discussion regarding whether receipt of the AdNull vector could limit the efficacy of the active agent.
- The informed consent document could be further improved by the following:
 - Simplification of technical terms that are primarily found in the tables
 - Inclusion of a discussion of any alternative experimental therapies, including dietary therapies, for which there is empiric data, especially since participants enrolled in the control arm are not expected to receive any clinical benefit from participation
 - Shortening the informed consent document used for the dose escalation phase by eliminating the description of the control arm, as that is not part of the dose escalation study
 - Removing any references to a therapeutic gene in the informed consent document, as such references may lead to therapeutic misconception

G. Committee Motion 2

Dr. Kohn summarized the RAC recommendations to be included in the letter to the investigators, expressing the comments and concerns of the RAC. No official motion or second was offered that these comments be approved by the RAC, but a vote of the RAC members was taken. The RAC voted to approve these summarized recommendations by a vote of 17 in favor, 0 opposed, 0 abstentions, and 1 recusal.

IX. Review and Discussion of Human Gene Transfer Protocol #1201-1143 titled: A Phase II, Randomized, Active Control, Open-Label, Multi-Center Study To Evaluate the Safety and Efficacy of EPODURE for Sustained Treatment of Anemia in Hemodialysis Patients

Principal Investigator: Geoffrey Block, M.D., Denver Nephrology Research
Additional Presenters: Stephen Bellomo, MsME, Medgenics; Anatole Besarab, M.D., Henry Ford Hospital; Marvin Garovoy, M.D., Medgenics; Philip Ng, Ph.D.,

Sponsor: Baylor College of Medicine; Amos Panet, Ph.D., Hadassah School of Medicine; Andrew L. Pearlman, Ph.D., Medgenics; Ehud Shoshani, M.D., Medgenics
RAC Reviewers: Medgenics Medical Israel, Ltd.
Drs. Fost, Hammarskjöld, and Kohn
Ad hoc Reviewer: Jeffrey Berns, M.D., University of Pennsylvania (*via teleconference*)

Dr. Fong was recused from discussion of this protocol due to a conflict of interest.

A. Protocol Summary

The investigators propose to conduct a Phase II study to test the use of EPODURE Biopumps to treat renal anemia in endstage renal disease (ESRD) patients on dialysis. EPODURE Biopumps are autologous tissue samples which are taken from the dermis (inner layer of skin) of the dialysis patient that will be treated. These tissue samples are exposed to a replication-incompetent helper-dependent adenoviral (HDA_d) vector, which is devoid of all native viral genes. This vector is engineered to carry the human erythropoietin (EPO) gene with a CAG promoter (a combination of the cytomegalovirus (CMV) early enhancer element and chicken beta-actin promoter). Transduction with the HDA_d-CAG-EPO vector is performed *ex vivo*, after which the tissue samples produce and secrete EPO. The amount of EPO produced *ex vivo* will be measured and an appropriate number of the Biopumps will be implanted in the research participant to provide steady, continuous delivery of EPO.

Since EPO is mainly produced by the kidneys, patients with kidney failure do not produce sufficient amounts of this protein. EPO is used by the bone marrow to enable the production of new red blood cells, and patients with insufficient EPO are anemic due to this insufficiency. This anemia is usually treated by injections of recombinant EPO produced in hamster ovary cells. Serial injections of EPO lead to dramatic changes in EPO concentration in the blood, and further cause difficulty in maintaining steady hemoglobin levels in the treated patients.

A previous Phase I/II clinical trial of EPODURE Biopumps was performed in Israel on predialysis chronic kidney disease (CKD) subjects and was shown to be safe and to provide 4 months or more of treatment of anemia without the need for supplemental injections of EPO. The proposed trial will be very similar to that trial, but will treat dialysis research participants and allow for titration of dose in each subject. The proposed clinical trial is a Phase II, open-label, randomized, multi-center, tailored and titrated dose study. In this study, dialysis research participants will be initially treated with EPODURE Biopumps that produce a dose of EPO similar to what the research participants previously received by injections. Blood samples will be drawn from the research participants to test the EPO concentration in their blood and the physiological effect on their hemoglobin levels.

B. Written Reviews by RAC Members

Twelve RAC members voted for in-depth review and public discussion of the protocol. Key issues included the novelty of the transgene and the clinical indication. Although at least two participants in the investigators' Phase I study have long-term (greater than 12 months) expression of erythropoietin from the Biopump, an adenoviral vector may not achieve consistently prolonged expression of a protein that is needed for chronic therapy. In addition, as it is not uncommon to adjust the dose of erythropoiesis-stimulating agent (ESA) administered based on the hemoglobin levels, the relative advantage of constitutive expression was deemed important to discuss. As adenoviral vectors are known to cause cytokine activation and an inflammatory response, the risks of using this vector in patients who are already at higher risk of infection should be reviewed.

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

Dr. Fost requested clarification of what happens after the six-month follow-up, especially whether the pumps will be left in if the EPO and hemoglobin levels are in an acceptable range and whether additional follow-up will be conducted as long as the pumps remain in place. He asked the investigators to discuss

the arrangements that will be made for research participants hospitalized at another location away from the investigators, and to delineate the data monitoring plan, particularly for SAEs. Dr. Fost suggested three wording changes for accuracy and clarity in the informed consent document.

Dr. Hammarskjöld asked the investigators to discuss evidence that the helper-dependent adenovirus (HDA_d) vectors have been demonstrated to exhibit stable, long-term transgene expression. In view of several studies in which adenovirus was shown to be capable of integration, she suggested that the investigators use assays to test for potential integration events in transduced cells before implantation. Although the investigators imply that several precautionary measures in the design of the vector will eliminate the risk of generating replication-competent adenovirus by recombination events, adenovirus genomes have been shown to have a high recombination rate, and Dr. Hammarskjöld remained concerned about the possibility of generating replication-competent virus; she asked whether viral stocks and/or transduced cells would be tested directly to exclude the presence of replication-competent virus. In addition, she asked whether all viral stocks would be tested for helper-virus contamination before use in transduction protocols, and what level of contamination would be deemed acceptable. Dr. Hammarskjöld noted that SCID mouse studies show secretion of EPO over several months and asked whether similar data are available from the ongoing human trial in Israel. Also regarding the ongoing Phase I/II clinical trial in Israel, she asked how long those research participants have been followed and the total number of participants dosed to date. Noting that Biopumps will be removed if hemoglobin levels are too high, Dr. Hammarskjöld asked the investigators whether the removed cells would be tested for the presence of the transgene, EPO RNA, and/or EPO secretion levels, and whether the cells also could be tested for evidence of integration and/or expression of adenovirus RNA. She also asked whether the Biopumps would be removed routinely at the end of the two-month follow-up period (which follows the four-month study period after transplantation). Because innate immune responses do not require viral transcription and, therefore, represent a special concern, Dr. Hammarskjöld asked whether the investigators plan to measure cytokine production and/or potential antibody responses to the vector. Regarding the informed consent document, Dr. Hammarskjöld suggested rewording one sentence for accuracy and clarity.

Dr. Kohn noted several potential benefits to this approach, the fact that previous human subject data from the Phase I and Phase I/II trials showed no SAE from the product, minimal biosafety issues from the use of the HDA_d, and no ethical, legal, or social issues in terms of vulnerable participants. He asked about the expected duration of persistence of cells expressing EPO and noted the need for concordant follow-up, and asked the investigators to describe the long-term monitoring plan that will be used. Although the investigators do not expect immune responses to virion proteins, whether such a response will occur is not known; Dr. Kohn asked, therefore, whether this potential response has been monitored in the Phase I/II trial and whether it should be monitored for this proposed Phase II trial. He asked the investigators to delineate the Study Stopping Rules with regard to number or severity of SAEs and/or the number of grafts that must be removed. Dr. Kohn noted that the informed consent document conveys appropriate information about the voluntary nature of participation, the experimental nature of the approach, and the procedures involved, and he offered three suggestions to improve clarity and accuracy.

Ad hoc reviewer Dr. Berns expressed concern that research participants could have high hemoglobin levels for many weeks or months given the trigger for Biopump removal and the rate at which dose reductions are made; he also was concerned that participants could have quite low hemoglobin levels for an extended period, and that the “rescue” aspect of the protocol may need to be more aggressive. He suggested the inclusion of a safety mechanism to account for the possibility of an initial period of lesser response followed by a return to increased responsiveness; if this occurs at the time when a new implant is placed because of inadequate initial response, an overly rapid increase in hemoglobin level is possible. Dr. Berns asked the investigators to discuss systemic (*in vivo*) factors that might modulate EPO protein synthesis by the transfected cells, whether bioavailability would be influenced by adiposity, and whether medications that might be distributed in skin would affect Biopump synthesis of EPO or its delivery into the circulation. He requested information about how Biopump removal would be managed and paid for if a participant is not under the care of the investigators or is hospitalized at a facility at which the investigators do not have medical staff privileges. If intravenous iron supplementation will be allowed during the study, Dr. Berns suggested that the circumstances be specified, in part to avoid rapid hemoglobin rise. He asked the investigators to discuss the basis for the assumption that the

pharmacodynamic response to intermittent EPO administration will be similar to continuous exposure, and he asked for clarification as to whether all Biopumps, regardless of level of persistent EPO synthetic activity, will be excised at study termination (or whenever an individual is otherwise last enrolled in the study). Dr. Berns wondered about the possibility that transfected cells from the Biopump could migrate or be carried via the circulation to distant sites and produce EPO in a location that would not be accessible for removal. He also asked whether stroke should be an explicit exclusion criterion for participation in this proposed study.

C. RAC Discussion

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

- Dr. Berns remained concerned that, if a research participant needs to be treated for iron deficiency, the Biopumps might need to be removed. He suggested that the protocol state this fact more clearly.
- Dr. Yankaskas asked about the procedure for Biopump removal.

D. Investigator Response

1. Written Responses to RAC Reviews

The investigators stated that they plan not to remove Biopumps that are no longer functioning *in situ*. After completion of six months of follow-up (four months of efficacy assessment plus two months of safety follow-up), research participants with functioning Biopumps will be followed in a six-month extended safety follow-up period as part of this trial and then will continue in a separate two-year open-label extension safety study. Participants will continue to be followed until their exogenous recombinant human erythropoietin (rHuEPO) administrations exceed 75 percent of run-in dose.

Regarding research participants hospitalized at a distance from the investigators, management will follow standard-of-care procedures such that emergency removal of Biopumps should not be necessary. Excessive hemoglobin levels, which are rare in this patient population, can be managed by phlebotomy if needed. Low hemoglobin level, which is the more common problem, is managed by rHuEPO administration or, in the rare case of an emergency, by blood transfusion. Research participants will be educated and provided with information cards that will enable them to properly notify the medical personnel wherever they are hospitalized, and to notify the investigator of their hospitalization. If Biopump removal is necessary while a participant is hospitalized, Medgenics will be responsible for the removal cost of all Biopumps.

The investigators agreed to modify the protocol to describe a safety monitoring plan, and an independent DSMB will be established to assist in monitoring participant safety. A charter will be written that describes the roles, responsibilities, and procedures of the DSMB.

The specific HDAd vector used to transduce the Biopumps has only been tested in humans in the current Phase I/II CKD EPODURE trial in Israel. Results from this study show elevation and maintenance of hemoglobin for 3 to 36 months, while EPO serum levels remained generally low. In addition, *in vivo* studies in which these human Biopumps have been implanted in SCID mice, have demonstrated more than six months of systemic secretion and delivery of EPO and elevation of hematocrit. Other researchers have published preclinical studies using direct administration of this same vector expressing other genes in animal models, showing that HDAd can mediate long-term transgene expression (up to six years) in liver, lung, muscle, brain, endothelial cells, and eye.

Adenovirus-based vectors have been reported to integrate randomly into the host cell genome at relatively low frequencies. The investigators do not plan to test for vector integration prior to Biopump implantation for the following reasons:

- Unlike retroviral or lentiviral vectors, adenovirus-based vectors do not inherently integrate.

- Since a Biopump contains approximately 1 million cells, from a safety perspective the chances that such a rare integration event would occur in a specific genomic site leading to oncogenic transformation are remote; thus, the investigators believe a negligible risk of oncogenic transformation exists as a consequence of such low integration frequency events.
- Adenovirus-based vectors have been administered into a large number of humans, including patients with cancers whose immune systems have been altered by radiation and/or chemotherapy; no instance of oncogenic transformation or any other genotoxic effect attributable to vector integration has been reported.
- In the ongoing Phase I/II CKD trial in Israel, no genotoxic effect attributable to vector integration was observed in 22 research participants implanted with transduced Biopumps for as long as three years.
- The implanted Biopumps can be removed quickly and safely if unforeseen issues arise, which provides an added level of safety.

All HDAd stocks will be tested for the presence of replication-competent adenovirus (RCA) as part of release testing, and the investigators will adhere to the FDA recommended specification of ≤ 1 RCA in a total of 3×10^{10} viral particles (vp). For the HDAd to be used in the proposed Phase II trial, RCA was tested and found to be undetectable at 3×10^{10} vp.

Helper virus contamination level will be ascertained for all HDAd stocks as part of their release testing, and only those that meet the strict specification will be used. The investigators will evaluate this specification when data are available from a reasonable number of additional production lots, and they will modify the specification based on that data.

Serum EPO levels were sampled at time points throughout the Phase I/II clinical trial in Israel, as was hemoglobin (the key clinical endpoint). No clear correlation was seen in any research participant between the EPO serum behavior over time and the corresponding duration of maintenance of hemoglobin by the implanted Biopumps. This finding comports with well-known experience that serum EPO levels do not predict nor are they parallel to hemoglobin levels.

In the Phase I/II CKD trial, 22 participants have been dosed in three dose groups. The longest follow-up has been approximately 20 months in a formal extended follow-up protocol, and approximately 36 months in off-protocol follow-up. Fourteen participants have been followed for more than six months, and seven participants have been followed for more than one year.

Histological slides will be prepared from all excised Biopumps, and will be analyzed by immunohistochemistry for expression of EPO protein. In addition, the investigators currently are validating methods using PCR to test for the presence of the transgene and expression of EPO RNA; these tests will be implemented when available for both studies of *in vitro* Biopumps and all excised Biopumps.

HDAd transduction of the Biopumps is performed *ex vivo*. Residual unabsorbed viral particles are removed from the Biopump by extensive washing prior to implantation, so the research participant is not exposed directly to high titers of HDAd viral particles. Innate response and antibodies against the vector are not expected, and have not been observed in the Phase I/II CKD trial.

In the ongoing Phase I/II EPODURE CKD trial, three research participants were implanted a second time with HDAd transduced Biopumps, and all responded with an increase in EPO levels similar to the response observed following their first Biopump implantations. These results indicate that a second implantation can be conducted safely with successful secretion of EPO. Medgenics plans to perform histological analysis for a cellular immune response in any Biopump excisions in the proposed Phase II EPODURE trial.

The investigators agreed to include a section in the protocol to describe the stopping rules, stating that all study agent administration will stop (all implanted Biopumps would be resected) if death occurred that was attributed to the study drug or if an EPODURE Biopump was removed due to a grade 3 or higher adverse event attributable to the study drug. All SAEs, regardless of relationship to EPODURE, will be

reported to the DSMB. The investigators stated that if the study drug is stopped, then all participants will continue to be followed for safety.

The EPO dose adjustment is consistent with the FDA label. The investigators noted that several studies have shown harm with hemoglobin targets of 13 g/dL or higher during ESA treatment sustained for greater than one year, but they indicated they were not aware of any data indicating harm for transient elevations of hemoglobin levels greater than 11 or 12 g/dL nor of literature to indicate that transient increase in hemoglobin during a 4-week period is harmful. Based on experience with the Phase I/II CKD study, EPODURE is expected to expose participants to significantly lower serum EPO levels compared to ESA injections, thereby mitigating risk of high EPO levels. This proposed study is designed to monitor hemoglobin closely, and participants will not experience high hemoglobin for many weeks or months.

If hemoglobin levels drop below 9 g/dL on two consecutive weekly assessments or falls below 8 g/dL on any single measurement, supplemental rHuEPO may be administered. Given that this study is the first to evaluate EPODURE in research participants on dialysis, the investigators explained that this protocol will not specify a dose of EPO for “rescue.” The protocol will allow the investigator to select the supplemental EPO dose based on the hemoglobin response to EPODURE and the investigator’s experience with the research participant’s prior EPO dose and response.

The implantation procedure and healing process are minimal and have been well tolerated by more than 20 participants in the Phase I/II CKD trial. No sign of hyporesponsiveness to EPO was observed. The implantation procedures may be considered comparable to skin biopsies under local anesthesia.

The investigators stated that they do not expect any drug effects on EPO secretion from the Biopump. However, they plan to collect data on concomitant medications and could conduct subgroup analyses on the study results. They have not investigated the effect of adiposity on EPO synthesis.

Given that this study is the first to evaluate EPODURE in research participants on dialysis, the use of the mean administered dose is merely the starting point to avoid overdose. The investigators plan to monitor EPO and hemoglobin response closely throughout the trial.

A typical Biopump contains roughly one million cells (mostly dermal fibroblasts), which upon *ex vivo* transduction incorporate gene copies capable of producing EPO. HDAd integration into the cell chromosomes is a rare event and there is no known mechanism for vector replication; therefore, the initial number of gene copies can only decrease over time, such as when cells die.

The investigators agreed to modify the protocol to exclude individuals with a history of stroke or transient ischemic attack. They also agreed to make the suggested changes to the informed consent document to improve accuracy and clarity.

2. Responses to RAC Discussion Questions

Following Dr. Hammarskjöld’s question about the possibility of integration and after reviewing the literature, Dr. Panet reported that the investigators decided to look for integration by examining the junction between the cellular and viral integration sites. The investigators will look first in the *ex vivo* Biopump, then at the SCID mice, and eventually at human tissue once tissue has been excised from research participants.

Dr. Ng explained that this system is different in that the material being implanted is not a virus. Therefore, with the extensive washing and with ten days in culture prior to implant, any unabsorbed vector would be removed. Data shows that reimplantation is possible.

Regarding the possible need for iron supplementation, Dr. Block stated that the investigators will clarify in the protocol that they will not administer additional exogenous iron unless a participant is below hemoglobin target and becomes iron deficient, and they will clarify the conditions under which the Biopumps would be removed.

Dr. Shoshani explained how the Biopumps are removed. The implant is located underneath two markings on the skin, which allows identification of the implant versus the surrounding tissue.

E. Public Comment

No public comments were offered.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

Preclinical Issues

- Although adenoviral vectors generally do not integrate, integration is possible if any replicating cells remain in the micro-organ implant. This potential safety issue can be examined by the following analysis of the micro-organs: 1) *ex vivo* tissue transduced with the helper-dependent adenoviral vector that expresses the gene for human EPO, 2) micro-organs that have been implanted into SCID mice, and 3) any micro-organs that are removed from research participants.

Clinical and Trial Design Issues

- Currently, the proposed long-term follow-up for individuals in this trial is 2 years. However, if there is prolonged expression of EPO from implanted micro-organs in any participant, the length of follow-up for such individuals should continue beyond 2 years.
- Prior to implantation, the micro-organs are washed extensively to remove any residual viral particles. Nonetheless, it is advisable to determine whether a given participant has preexisting immunity to the adenovirus, as this might lead to an immune response if there are any residual viral particles. Also, monitoring participants for increases in antibody titers to adenovirus after receiving micro-organ implants may provide useful information about the development or absence of immune responses to the vector that could impair multiple implant procedures. These data will inform the safety and efficacy analysis.
- A DSMB should be added to oversee this trial. The DSMB should impose the following stopping rules to improve the safety of this study: 1) a death that is attributed to the study drug and 2) removal of all micro-organ(s) if a serious adverse event occurs that is attributed to the study drug and is Grade 3 or higher, as measured, for example, by the Common Terminology Criteria for Adverse Events.
- Intravenous iron supplementation is permitted in this trial. It is possible for the hemoglobin level obtained after implantation of the micro-organ to be stable and within the desired range but for iron indices nonetheless to indicate iron deficiency. The protocol should address explicitly whether intravenous iron will be adjusted in this case, including a discussion of the risks of continuing iron supplementation that may lead to an overcorrection of the hemoglobin level. Overcorrection may necessitate removal of one or more micro-organs and, therefore, it is important to have uniform criteria for addressing this situation.

Ethical, Social, and Legal Issues

- As part of the informed consent process, participants should be made aware that integration of the vector, while highly unlikely, could have longer-term clinical effects that might not be observed for several years. Examples of these clinical effects are skin lesions or abnormal growths. Therefore, it is important not only to investigate any unusual skin growths, especially in the vicinity of the micro-organ implantation, but also to ensure that a participant's primary care provider is aware of his/her participation in this study.

- The following clarifications should be made to the informed consent document:
 - Substitution of the more specific term, rHuEPO injections for ESA, as there are several medications in this class
 - Specifying this is a disabled cold virus rather than a disabled influenza virus
 - Providing additional details on the risks associated with elevations of EPO
 - Replacing the term “pregnancy aftermath” with language that more specifically indicates that this refers to information on the health of the newborn and any complications of pregnancy

G. Committee Motion 3

Dr. Kohn summarized the RAC recommendations to be included in the letter to the investigators, expressing the comments and concerns of the RAC. No official motion or second was offered that these comments be approved by the RAC, but a vote of the RAC members was taken. The RAC voted to approve these summarized recommendations by a vote of 18 in favor, 0 opposed, 0 abstentions, and 1 recusal.

[At this point, Dr. Fong resumed chairing the March 2012 RAC meeting.]

X. Update Discussion Regarding IBC Review of Low Biosafety Risk Protocols

Presenter: Dr. Corrigan-Curay

A. Presentation

Dr. Corrigan-Curay summarized the IBC's role in reviewing human gene transfer, discussed the feedback received by the OBA, and presented the status of the proposal to exempt from IBC review certain multisite, low biosafety risk gene transfer trials. The proposal was provided by the RAC Working Group.

The role of IBC review in human gene transfer trials is to identify and manage biosafety issues raised by gene transfer agents, including horizontal or vertical transmission risk, safe handling and administration, ensuring that the informed consent document incorporates information regarding risks that arise from the biological nature of the agent, examining the preclinical animal data that support the safety of the vector, identifying new biosafety issues through analysis of adverse event reports, and, for protocols that undergo in-depth public review by the RAC, ensuring that the RAC recommendations are considered.

Feedback from some investigators regarding IBC review of multisite trials has noted that a number of gene transfer clinical trials are conducted using vectors for which there is considerable clinical experience and for which the biosafety risks are well characterized. Multiple individual IBC reviews of low-risk trials may add little benefit to protect public health and can be costly. The conclusion of the RAC Working Group was that a mechanism to streamline the review of low-biosafety-risk trials is needed to facilitate research, especially for multisite trials.

As a result of this feedback, OBA is considering exempting certain multisite Phase II or Phase III low-risk trials from IBC review. IBC review would not be required if the vector is a plasmid or a specified non-integrating vector derived from a Risk Group 2 virus and if a previous safety study in humans tested the dose proposed for the Phase II or Phase III study. In addition, an initial safety trial with the specific vector and transgene should be comparable in terms of trial design and target population. Viral vectors derived from the following viruses are eligible: adenoviruses, herpes simplex virus, poxviruses except for vaccinia, and adeno-associated viruses. Viral vectors eligible for exemption must be attenuated—shown to be less pathogenic compared to the wildtype virus in both animal models and the previous safety study in humans. Attenuation may be achieved by gene deletions or irreversible mutations in genes required for cell-to-cell transmission or virulence.

Multisite trials proposed for exemption from IBC review must use one of the specific vectors eligible for exemption, and an initial safety study must have been completed. The multisite trial must use the same delivery method, comparable concomitant interventions, and the same dose as tested in the Phase I trial. The multisite trial's target population must be comparable to the safety study in age and infectious disease burden. If the multisite trial will enroll pediatric research participants, the safety trial must have enrolled pediatric participants at the dose to be tested. The RAC Working Group also recognized that the safety of an agent may differ if significantly different prevalences of chronic infectious diseases exist in the population to be studied. In addition, exemption depends on there having been no evidence in the safety study of vertical or horizontal transmission of the agent. Dr. Corrigan-Curay showed decision matrices for exemption based on the existence of an initial safety trial and comparable population.

A decision that a trial meets the exemption criteria will be made by the relevant IBC. At institutions that have an IBC, the principal investigators should provide sufficient information for the IBC to determine that the trial does not require IBC review. A decision that the trial meets the criteria for exemption also can be made by the biosafety officer in consultation, as needed, with the IBC chair. An IBC also can decide to accept a decision made by another IBC regarding exemption. Institutions can develop their own policies to review exempt protocols, but such policies would be determined by the institution and would not be required under the *NIH Guidelines*. Investigators who conduct a trial at an institution that has an IBC should notify the IBC that the trial will be conducted but that it is exempt from IBC review; doing so allows the IBC to be aware of the trial's existence and to understand why they are not being consulted.

Once an IBC determines a trial is exempt from IBC review, an IBC is no longer required to be established at sites that do not have one, such as sites not funded by NIH. If the trial will enroll participants at sites both within and outside of the United States but the safety study was conducted only in the United States, the U.S. sites can be exempt from IBC review but the international site should have an initial IBC review in accordance with the local rules of that country or the *NIH Guidelines*.

A trial that meets all the above criteria could be exempt from IBC review under the *NIH Guidelines*, although an IBC retains the discretion to review the trial in accordance with institutional policy. Though exempt, the protocol would still be required to register with OBA in accordance with the requirements of Appendix M, and the principal investigator would remain responsible for all reporting requirements under Appendix M such as adverse event reporting and annual reports. Reporting to the IBC would not be required under the *NIH Guidelines*, but institutions could establish their own reporting requirements.

B. RAC and Public Discussion

Dr. Corrigan-Curay clarified that vaccine protocols would be included in this rule change.

Discussion ensued about whether shedding studies would be required. Dr. Takefman noted that some transient shedding by DNA is likely to occur when using AAV. He explained that the FDA's Office of Vaccine, Blood, and Biologics typically does not ask for shedding studies. For gene transfer, the FDA has been moving away from requesting shedding studies for Phase I studies of replication-incompetent, low-risk viruses because, in many cases, shedding occurs but is transient shedding that lasts only a few days. The FDA's primary concern about shedding is in dealing with licensure and getting that information on a product label; it is not a public health issue. In the future, shedding data will not be available because the FDA will no longer require shedding studies. Dr. Fong added that clinical evidence, rather than viral shedding data, should be the standard. Additional discussion centered on alerting participants and their families about infection control, vertical versus horizontal transmission, precautions or instructions for preventing transmission, studies looking for DNA that are likely to find DNA that may not be intact and thus may not be transmissible, and the fact that clinical sequelae from shedding to third parties has not been encountered.

The RAC concluded that because regulatory bodies oversee these protocols, long-term follow-up is required, and other groups or individuals review these trials and their results, an additional review by an

IBC would not be necessary, and evidence of vertical or horizontal transmission would not be a criterion to prompt an IBC review.

Dr. Claudia Mickelson, via teleconference from the Massachusetts Institute of Technology (and a former RAC chair), wondered what would happen if a disagreement occurred among IBCs as to whether a trial is exempt or not, especially if a multisite trial included sites that were funded by NIH and sites that were funded by other sources. Dr. Fong responded that, if a trial is exempt under the *NIH Guidelines* but an IBC chooses to review that trial, doing so is the choice of the IBC, and NIH would not stop an institution from being rigorous. He stated his belief that this situation will arise very infrequently. Dr. Corrigan-Curay explained that the Working Group recommendations attempt to streamline the process of determining exemption. She added that OBA is available to answer questions when investigators receive conflicting information from IBCs about exemptions or when IBCs have questions about exemption, and she agreed to insert language emphasizing OBA's availability for guidance.

Dr. Fong noted that when the gene transfer field first started about 25 years ago, many important safeguards were instituted to reduce the chances of SAEs occurring. As more experience is gained with certain vectors, agents, and diseases, some of those safeguards may need to be scaled back because they become obstacles to research progress. However, the RAC needs to hear the possibilities of how these changes could lead in unforeseen ways to new problems.

C. Public Comment

1. Dr. Barney Graham, chief of the Clinical Trials Core at the Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases (NIAID)
(presented in person on Day 1)

Dr. Graham discussed a proposal to the RAC from NIAID about how to deal with DNA or replication-defective vectors delivering vaccine antigen genes. VRC has been involved in gene delivery vaccine studies since the late 1980s. VRC has conducted these studies for decades, and tens of thousands of people have been immunized with these vectors, with no alarming results. In addition, FDA issued guidance on DNA vaccines in 2007 that states that clinical toxicology tests do not need to be repeated as long as the proposed trial will use the same vector backbone.

VRC proposes that the RAC adopt the same exemption criteria used in Appendix M for IBC review of clinical protocols. Clinical protocols using these products have been reviewed by IBCs at the bench level and at the preclinical testing level, and by the time they get to the clinical trial level they have been reviewed on more than one occasion by an IBC. The clinical trial level includes an IRB review, an FDA review, a sponsor review, and several other reviews to ensure good clinical practice, so IBC review is no longer necessary. IBC review under these circumstances adds nothing to safety, and it involves IBC time and attention that could be focused on other issues, constituting an enormous waste of resources and a burden to all involved.

IBC reviews should no longer be required for gene-based vectors, either DNA or replication-defective viral vectors that express vaccine antigen. These vectors will be cleared from the subject, and do not represent harm to the environment, the laboratory or clinic personnel, or the vaccine volunteer.

2. Ms. Mary Enama, protocol operations manager at the Vaccine Research Center, NIAID

Ms. Enama proposed that a trial be exempt from IBC review, whether the trial is to be conducted at a single site or at multiple sites, if at least one safety study in humans has been conducted successfully. She noted that products that have been used in a multicenter study sometimes cycle back to a single site study for various reasons. One example is the canary pox vector HIV vaccine, which was part of a regimen in the RV144 Thailand trial and is the only regimen that has shown any level of efficacy in HIV in more than 25 years of research. The canary pox vector vaccines have been in clinical trials for approximately 15 years. In addition to having gone through a Phase I human trial, the same type of canary pox vector vaccines have been approved by the U.S. Department of Agriculture as veterinary

vaccines and are used in veterinary clinics and barns around the world. A time comes when some products reach a level at which many safety assessments have been conducted. Those products should be exempt completely from IBC review. Whether a product is being used in a multisite trial should not be the limiting factor regarding IBC review.

Discussion ensued regarding possible exemption from IBC review for single sites. Dr. Kohn pointed out that a single-site trial must be reviewed by an IBC, although Dr. Corrigan-Curay clarified that IBC exemption can be decided at an abbreviated IBC meeting, which speeds up the approval process.

3. Dr. Jan Vleck, IBC Services (via email)

Dr. Vleck supports removing the criterion of no evidence of horizontal or vertical transmission as an IBC function. Comparatively few of the investigator brochures give definitive information from animal studies about the presence or absence of vector in the gonads or semen. This is the case even with replication-competent or potentially integrating vectors. Similarly, it seems rare to see preclinical information about horizontal transmission looking at cage mates, etc. The presence of this language seems to assign responsibility to the IBC for asking for and evaluating evidence about shedding or transmission, and there will be vast inconsistency about how this is done. Once an IBC determines a trial is exempt from IBC review, is there some expectation of an unaffiliated determination or would a sponsor's internal IBC determination be acceptable? What if there is diversity of IBC determination?

Dr. Corrigan-Curay responded that investigators should notify other IBCs when conducting a study at their institution. For diversity of determination, OBA could assist. Dr. Fong noted that the criteria for exemption are spelled out clearly, so IBC determinations should be relatively consistent.

XI. Discussion of Results on OBA Protocol #0704-849 titled: A Phase I Study Evaluating the Use of Allodepleted T Cells Transduced with Inducible Caspase 9 Suicide Gene After Haploidentical Stem Cell Transplantation

Presenters: Helen Heslop, M.D., Baylor College of Medicine, and Cliona Rooney, Ph.D., Baylor College of Medicine

A. Presentation by Dr. Rooney

Dr. Rooney discussed the preclinical development of a human inducible suicide gene. With increasing use of T-cell therapies, Dr. Rooney and colleagues are focusing on the potential toxicities of those therapies. The purpose of the suicide gene is to eliminate a cell therapy should it prove unexpectedly toxic. For T-cell therapies, major toxicities might be expected from the toxicity of transgenes in genetically modified T cells or from the toxicity associated with retroviral integration. Increasing the specificity of T cells specific for nonvirus tumors could induce autoimmunity. With frequent use of allogeneic donor lymphocytes to improve immune reconstitution after allogeneic bone marrow transplant, there is risk of graft-versus-host disease (GVHD). A strategy to eliminate cells that are inducing toxicity would increase the safety of the therapeutic process.

A suicide gene must be expressed in all cells that express the therapeutic transgene. If not associated with a therapeutic transgene, for example in GVHD, a selectable marker is used to select the cells expressing the suicide gene. Because a suicide gene can kill a cell, it must have low basal toxicity, it must kill the cell only under the appropriate circumstances, it must have high specific activity, and it must be nonimmunogenic.

Initially in 2000, the only available suicide genes were the herpes simplex virus thymidine kinase gene and the *E. coli* cytosine deaminase gene. Both of these genes are immunogenic because they are foreign to the body, and immune responses to the genes can eliminate the cells that are expressing them—an undesirable outcome. A significant problem with the thymidine kinase gene, which is commonly used, is that it is dependent on ganciclovir for activation and, therefore, ganciclovir cannot be used as a

therapeutic drug, which is an important use for treating cytomegalovirus after bone marrow transplant and in other circumstances. In 2000, David Spencer, Ph.D., in the immunology department at the Baylor College of Medicine, was interested in molecules whose activity was induced by dimerization; among those molecules are the caspase genes.

The caspase pathway is important in extrinsic and intrinsic induction of cell death in response to many different stimuli, including stress. Dr. Rooney and colleagues were interested in the downstream caspase molecule because these molecules were thought to be resistant to many of the anti-apoptotic molecules. They evaluated these molecules as inducible caspases in T cells by fusing a caspase molecule to two FK-binding domains, then inducing apoptosis in T cells by use of a dimerizer. These researchers determined that the most effective caspase molecule was caspase 9, although some problems arose initially. Dr. Clooney described the development of a retroviral vector system and studies in which the gene transfer of inducible caspase 9 (iCasp9) domain eliminated cells.

Preclinical safety evaluation of iCasp9 produced no changes in T-cell phenotype, no changes in T-cell specificity, no clonal outgrowth, and the T cells' continued dependence on regular antigenic stimulation and growth factors for continued growth *in vitro*. In general, preclinical studies showed that expression of iCasp9 does not alter the phenotype or function of the cytotoxic T cells (CTLs), and activation of the modified iCasp9 gene eliminates up to 90 percent of total and 100 percent of functional transgene-expressing CTLs. In contrast to the inducible Fas gene, which other investigators had suggested as a potential suicide gene, the iCasp9 is still functional in cells that overexpress the anti-apoptotic protein B-cell lymphoma-extra large.

B. Presentation by Dr. Heslop

Dr. Heslop discussed the Phase I study using the iCasp9 suicide gene, OBA Protocol #0704-849. The researchers used allodepleted T cells after a haploidentical stem cell transplant (HSCT; a transplant from a donor who is half a match), thus producing a significant risk of GVHD. One commonly used strategy is to infuse CD34 selected cells, which provides rigorous T-cell depletion and thus avoids GVHD but also removes the T cells that mediate graft-versus-leukemia (GVL) and antiviral activity. Dr. Heslop and colleagues have been interested in adding back T cells that are responsible for GVL and antiviral responses while removing the alloreactive cells that cause GVHD.

The primary aim of this study was to determine the highest dose of iCasp9 expressing allodepleted T cells that could be administered while limiting the severe Grade 3 or Grade 4 GVHD to less than 25 percent; secondarily, the study sought to obtain information on the biological and clinical effects of administering the dimerizer AP1903. Ten research participants have been enrolled on this study. Three participants have received allodepleted T cells at 1×10^6 cells/kg, two have received 3×10^6 cells/kg, and five have received 1×10^7 cells/kg. Four of these ten participants developed Grade 1 GVHD and received the dimerizer.

Dr. Heslop presented data on two of the participants who received the allodepleted T cells. Upon examination of the peripheral blood cells of the first participant who received the T cells showed an increase in the cells co-expressing CD3 and CD19. At the same time, this individual developed an increase in bilirubin and a skin rash consistent with GVHD, so he received the dimerizer. After administration of the dimerizer, he experienced a decrease, within 30 minutes, of about 90 percent of the T cells and a further decrease 24 hours later. Coincident with this fall in the circulating T cells, the investigators saw a rapid reduction in the bilirubin back to normal within 24 hours, and this individual's skin rash resolved in about 1 day. Continued follow-up of this individual saw a gradual increase in CD3- and CD19-positive cells, which presumably reflected the non-alloreactive population, which was not activated at the time he received the dimerizer. Although his T cells increased again, his bilirubin remained negative and he did not develop GVHD.

A second research participant received a second dose of cells (after FDA approval) because she had persistent mixed chimerism. She developed a rash that, on biopsy, showed GVHD. She received the dimerizer and subsequently experienced a rapid fall in recirculating CD3 and CD19 double-positive cells

30 minutes post infusion, with a further decrease at 24 hours; the following day her rash almost completely resolved. Using semi-quantitative PCR to detect the transduced T cells, the investigators discovered that both research participants showed a similar pattern, with a rapid fall in cell number after receiving the dimerizer.

Dr. Heslop summarized the experience with giving the dimerizer to research participants who developed Grade 1 GVHD in this study. Cells that express iCasp9 can persist and expand *in vivo*. When research participants developed GVHD, treatment with a single dose of the AP1903 dimerizer rapidly ablated the alloreactive suicide gene expressing cells, with resolution of acute GVHD in all four participants dosed. Additional questions include whether these transduced T cells persist long term in research participants who do not develop GVHD and whether their T-cell receptor repertoire is polyclonal. For one participant who did not develop GVHD, the infused cells expanded and then persisted for a considerable time after transplant. For some participants with long-term follow-up, cells that express CD3 and CD19 at 6 months and at 24 months continue to be detected. The researchers have examined all the participants for polyclonality and have found that the cells are polyclonal.

Dr. Heslop and colleagues treated 10 research participants with allodepleted T cells genetically modified with the suicide gene, all of whom had high-risk hematologic malignancies. Three of those individuals subsequently relapsed and died of their primary hematologic malignancy. The other seven are alive without relapse between 5 and 29 months after receiving T cells. Conclusions from this clinical trial are that:

- iCasp9 expressing allodepleted T cells can expand *in vivo*.
- Treatment with a single dose of the AP1903 dimerizer rapidly ablates iCasp9 T cells with resolution of acute GVHD.
- After AP1903 treatment, residual iCasp9 T cells re-expanded in the absence of further GVHD.
- Residual iCasp9 T cells show a polyclonal T-cell receptor repertoire and antiviral activity was retained after dimerizer treatment for acute GVHD.
- Antiviral activity was retained after AP1903 treatment for GVHD.

Future directions for this research include a follow-up study in which the infused T cells will have a simpler manufacturing methodology, not including *in vitro* allodepletion. The cells will be expanded and the investigators will rely on the suicide gene to eradicate the cells if the research participant develops GVHD. The investigators plan to incorporate iCasp9 in constructs for first-in-human studies with third-generation chimeric antigen receptors, and a few preclinical studies are underway using mesenchymal stem cells in lung cancer. In addition, Dr. Heslop said that the investigators propose to use iCasp9 as a safety mechanism.

C. RAC Discussion

Dr. Fong asked about the obstacles and opportunities to collaborate with other groups who want to use this strategy as a safety mechanism. Dr. Heslop noted that since publication of their paper on this topic, the investigators have received many requests from other investigators to receive the constructs to begin their own preclinical studies. The original developers of the vector have sent out the vector to several groups. A few groups have visited the investigators' manufacturing facility to watch the process in more detail, with the aim of implementing it at their own facilities. Investigators who want to obtain the dimerizer must discuss with the licensing company (Bellicum Pharmaceuticals) how to obtain it. Dr. Rooney explained that Baylor has a clinical-grade gene vector facility in which the vector can be manufactured on a contract basis.

Dr. Fong asked about the business model for the cassette and the suicide mechanism. Dr. Heslop responded that David Spencer, who developed the original dimerization strategy, has a company called Bellicum Pharmaceuticals that has obtained funding from the Texas Cancer Research Foundation to further develop this approach. Dr. Spencer is in discussion with his clinical trial collaborators at MD Anderson Cancer Center to develop a trial that would move the suicide gene toward later-stage applications.

In response to Dr. Hammarskjöld's query, Dr. Heslop stated that no one has tried yet to use caspase 9 as a strategy for cancer therapy.

XII. General Public Comments

A. Statement of the American Society of Gene and Cell Therapy (ASGCT)

Presented by Xandra Breakefield, Ph.D., Massachusetts General Hospital and president-elect of ASGCT

Dr. Breakefield read the following statement on behalf of the Board of Directors of the ASGCT.

The RAC was formed in 1974 to advise the NIH Director on the conduct and oversight of research involving recombinant DNA, as well as to serve as a public forum for discussion of these issues. In the 1990s, the RAC came to serve as an arbitrator of all clinical protocols in gene transfer, with the authority to approve or disapprove these trials in consultation with the NIH Director. In 1995 Dr. Harold Varmus, then NIH Director, requested an *ad hoc* expert review committee to assess "the changing role of the RAC, the way it may need to modify its operations, and how it should function to coordinate and facilitate productive gene therapy research." At the time, these experts recommended that the RAC review in public only those protocols thought, by a subset of RAC members, to have potential issues of concern. They also recommended that the RAC no longer have a regulatory role in the decision as to whether protocols would move forward, because that regulatory function was deemed to be amply provided by the FDA as well as by IRBs and IBCs.

In the intervening 16 years since that 1995 review, investigators in the field of gene therapy and administrators in these regulatory agencies have become highly knowledgeable and experienced in reviewing these protocols, with thousands of trials having been conducted worldwide and many showing promising benefit. The ASGCT believes, therefore, that it is time to reevaluate the mission and *modus operandi* of the RAC to better serve the needs of the research community and public.

The scientists and physicians in ASGCT fully acknowledge the important role the RAC has played in the development of these new medical therapies during their transition from basic research to clinical trials. In particular, the RAC has excelled in identifying specific areas of experimental research that benefitted from further in-depth discussions, and they have been instrumental in assembling knowledgeable groups of investigators to present and discuss these topics in open forums.

Based on the extensive safety data in the field now approaching 20 years, with many protocols using well-established agents that have been reviewed frequently by the FDA and with many delivery protocols no longer considered novel, the ASGCT Board of Directors believes the RAC would serve a more effective function by focusing on broader issues encountered by the field rather than on review of individual protocols.

Our recommendation is in line with the mandate of the RAC to advise the NIH Director on issues of concern to the public, which historically have been potential modification of the human genome at the germline level and the risk of creating and disseminating novel transmissible pathogenic agents. With respect to the gene transfer community, neither of these issues has been a problem with the commonly used gene therapy vectors employed today. In fact, to the contrary, after 20 years of testing and more than 1,000 trials, no evidence exists to support the current regulatory burden the RAC requests from gene transfer protocols.

Based on these considerations and response to deliberations by an ASGCT panel of experts, the ASGCT Board of Directors unanimously voted at a recent meeting to approve the following recommendation: The RAC should terminate review of individual clinical protocols and should instead identify new areas of research that require a public forum for discussion and review.

B. Public Comment

During his earlier presentation, Dr. Crystal offered the following comment: “Having a 20-year experience with this Committee, I think the RAC is enormously useful. I do not agree with the ASGCT; I think it is very useful for the field. Gene therapy is something special, something that society does not quite yet fully understand. The RAC provides all of us with peer review that is useful not only for the investigators but also for our IRBs. I am a supporter of the RAC and I think it should continue.”

Several public comments were submitted via email. Comments in support of the ASGCT statement were submitted by Dr. Carter, Carter BioConsulting, Dr. Schaffer, University of California, Berkeley, Dr. Rossi, City of Hope, Dr. Messer, Wadsworth Center, Dr. Bonini, San Raffaele Scientific Institute, Italy, and Dr. Wagemaker, Erasmus University Medical Center, The Netherlands.

Dr. Scott McPhee, Asklepios Biopharmaceuticals, Inc. supported modifying the role of the RAC to focus on providing guidance and educational meetings that focus on clinical trial issues, promoting a harmonization framework to support international review of clinical trials among FDA, EMA, and national agencies in non-U.S. countries, an issue for orphan disease research, and continuing to maintain the GEMCRIS database with greater scientific and public dissemination of regular reports on adverse event patterns or potential safety concerns

Several comments disagreed with the ASGCT statement and stressed the value of RAC review and reporting to the gene therapy field. Dr. Ertl and Dr. Zhu, Wistar Institute, stressed the importance of the public forum for discussion of planned clinical trials and adverse events provided by the RAC. Dr. Ertl also noted that the board of directors’ argument that gene transfer leads neither to germline transmission nor release of recombinant virus into the public takes an unduly narrow view of the risks of gene transfer, especially regarding future protocols that may aim to modify regulatory DNA sequences.

Dr. Dewhurst, University of Rochester, and Dr. Mickelson, Massachusetts Institute of Technology, commented on the public trust engendered by public RAC review. Dr. Dewhurst believed it would be a mistake to cease review of individual protocols because the transparency gained through RAC review of individual clinical protocols has resulted in greater public trust of recombinant DNA research as well as higher quality science, a benefit that would potentially be lost if the RAC were to abandon its review of individual protocols. He noted that having spoken with colleagues who work in other fields, he learned how uniquely valuable the RAC is because it provides an open forum for robust discussion of data, risks, and protocol-specific concerns. In doing so it has raised the bar for an entire field, helped inform key stakeholders, and built a trust that should not be taken for granted. Dr. Mickelson expressed her strong support for the NIH RAC and the role it has played in ensuring public access to information and data, and in enhancing the public understanding of the scientific and ethical complexities surrounding this unique area of research. The RAC provides the only mechanism for the open, peer, and public review and discussion of novel gene transfer research, research outcomes, and adverse events. The committee’s reviews and recommendations have served both to improve and support this clinical research. It would be a mistake for the research community and professional societies to underestimate the importance of this committee in fostering public acceptance of gene therapy research in their drive to try to reduce the regulatory process associated with the development of clinically relevant therapeutics.

Two former presidents of the ASGCT and RAC members expressed views in support of the RAC’s role. Dr. Friedmann, University of California, San Diego, noted that in light of the growing confidence in the safety and efficacy of some current gene therapy approaches and the urgency of moving these successes to additional disease models, it is reasonable for the ASGCT leadership to suggest changes in the review function of RAC in an attempt to facilitate the oversight of clinical protocols and speed the development of additional therapies. However, ending RAC review of clinical protocols may not be an ideal way to achieve these goals. RAC review of selected clinical protocols is an important way to perform exactly the functions recommended by the ASGCT—identifying important research questions of safety and efficacy and of public interest in many emerging technologies of gene transfer research and gene therapy. The ASGCT proposal does not underscore an important need for the oversight and regulatory communities and ASGCT to reevaluate, refine, simplify, and improve current practice. For now, that

should be done without eliminating the proven practice of protocol review. Dr. Kohn, University of California, Los Angeles, disagreed with the recommendation of the ASGCT Board and pointed out that the RAC reviews of clinical protocols are of high value in the majority of cases and are not significantly time limiting for most well-developed protocols undergoing the myriad other regulatory reviews. Many clinical trials of gene therapy are first-in-human experimental procedures involving complex molecular manipulations in research participants. Even most industry-sponsored trials are conducted at academic medical centers that receive public support, and those activities should be held responsible to the general public review. There is less local expertise for regulatory review of trials conducted at new sites, especially private clinics and non-academic-affiliated hospitals. RAC review of protocols provides a knowledgeable single-source entity to cite precedence and best practices and to provide guidance to local committees. He noted another important benefit to the field that would be lost. The centralized database, GEMCRIS is a valuable source of information to assess new complications that arise and to place them in the context of precedence.

C. RAC and Public Discussion

Dr. Buchmeier opined that the RAC would prefer not to review routine protocols; however, some protocols are important to review in detail and the RAC provides the expertise to accomplish that review. Relying solely on local IBCs or IRBs to do so is not wise because those committees vary significantly in composition and competence. He stated that the act of preparing a protocol for RAC review is a learning experience for investigators who do not have much experience with these protocols.

As an ASGCT board member, Dr. Heslop expressed her support of Dr. Breakefield's comments. As an investigator, she offered her appreciation of the RAC's significant contributions to the field, with RAC reviews having helped her protocols individually and having assisted the field overall. However, with the collective experience of more than 20 years, the need to review every new study no longer exists. The RAC plays unique and important roles in allowing discussion of events, ongoing studies, and across studies, providing unique information to researchers and the public. These roles should continue, and the RAC should focus as well on other areas of research that will benefit from a public forum for discussion and review.

From a personal perspective, Dr. Breakefield suggested that the RAC devise some method of separating protocols that need to submit a summary from those that need to submit full paperwork. The RAC could review all the protocol summaries and ask for full paperwork only on these deemed necessary. She noted the significant amount of time and effort being put into many protocols that do not require RAC review.

Dr. Kohn agreed that "triaging" all protocols to determine which ones require what level of review could be helpful. He noted, however, that the RAC application is not a significant additional burden to the applications required by other bodies. The burden consists primarily of Appendix M, which could be shortened for more standardized agents.

Dr. Kiem expressed his appreciation of possible efforts to streamline the process, and explained that the RAC is already trying to do this by selecting for public review only those protocols deemed by RAC members to raise important issues. As a chair of his institution's IBC, he noted that the IBC is helped significantly by the existence of a RAC review. In addition, Dr. Kiem shared that he had the impression that RAC review facilitated and sped up FDA discussions.

Dr. Breakefield reiterated that ASGCT wants to have a detailed, open discussion about this issue with RAC members. IBCs and IRBs look to the RAC and OBA regarding new issues that need discussion. However, RAC procedures would benefit from simplification, with the goal of moving the field forward faster and getting effective therapies to patients faster. Dr. Breakefield expressed the ASGCT's hope that a RAC meeting be devoted to this topic.

Dr. Fong welcomed the dialogue about the RAC process, noting that some institutions do not have resident expertise on gene transfer but protocols nonetheless will be conducted there. The RAC is an important resource to ensure that those protocols are reasonable and safe, and to safeguard the public.

However, if a vector, for example, is used routinely, some process should be available to eliminate the need of an investigator to file an Appendix M application. The Appendix M process should be simplified.

Also welcoming this dialogue, Dr. Chiocca noted the importance of recognizing the underlying sentiment, which has been expressed not only by the ASCGT but also from vaccine researchers who want to eliminate review of all vaccines. He acknowledged that the gene transfer field has evolved, and the RAC should address the possibility that its processes are viewed as an obstacle.

Dr. Corrigan-Curay acknowledged that the RAC has evolved over time, in part to minimize burdens, to keep pace with recombinant technology and emerging understanding. One example of attempts to minimize burden was to harmonize reporting with FDA so investigators can report in the same format to both FDA and OBA/RAC. She pointed out that while Appendix M submission is unique to RAC, it is less burdensome than perceived since investigators are encouraged to reference their protocols or their previous Appendix M submissions if there are no significant changes. In the clinical area, Dr. Corrigan-Curay stated that OBA continues to believe that a direct and immediate benefit to design and conduct of individual novel protocols derives from public RAC review. This benefit applies to the reviewed protocol and to other investigators developing similar protocols, as well as to the quality of IRB and IBC reviews. In addition, continued review and ongoing data reporting on these protocols provides transparent knowledge that helps move the gene transfer field forward.

Dr. Dresser noted that few people or organizations were aware that this issue would be brought up at this RAC meeting, so no patient advocacy groups or representatives of the public have had an opportunity to comment. Consideration of this issue requires a broader forum.

Dr. Takefman stated for the record how the RAC has been helpful to FDA, primarily through public dissemination that allows FDA to reference to investigators and sponsors the clinical issues and adverse events that were discussed publicly. Because most of the protocols selected are novel, challenging, and/or potentially controversial, having the RAC and its *ad hoc* experts discuss these protocols is helpful for FDA, especially because most of these discussions take place in early in the process of clinical development. Because FDA has 30 days from receiving a new IND submission to decide approval, being able to draw on a previous RAC discussion helps inform that process.

As a former IBC chair at the University of Virginia, Dr. Hammarskjöld relayed her experience. Her IBC received great benefit and helpful guidance from the RAC because the University of Virginia does not have many gene transfer investigators and, therefore, relatively little knowledge about research in this field. RAC review continues to be important for IBCs, although maybe not as important for the IBCs at institutions that have multiple gene transfer trials and extensive knowledge of this field.

Dr. Sarzotti-Kelsoe opined that the RAC does not significantly slow down the clinical trial process. The RAC publicly reviews only 20 percent of the submitted protocols, so there is a quick initial exclusion of 80 percent of protocols, which streamlines the process. She agreed that shortening the process associated with Appendix M submission might be helpful.

Dr. Chatterjee stated that the RAC provides an important public forum, and that maintaining the public database also is important. She agreed that the RAC's protocol review process could be streamlined further but also noted that the review process is not an onerous task.

D. Concluding Remarks

Dr. Fong concluded RAC comments on this issue by offering the following statement.

The gene transfer field includes no approved therapy. Any "bad event" that happens in this field affects everyone and, therefore, it is important to have in place enough safeguards so the public can trust that the appropriate actions have been taken if something bad happens. If the gene transfer field had many approved therapies and many vectors already in clinical use and everyone knew how to use them, the RAC could be disbanded; such is not the case.

The gene transfer field has evolved and some of the science is now known, but it remains important to safeguard against those protocols that are proposed to be conducted at institutions where that knowledge is not as well known. Most IRBs and IBCs do not have the necessary level of expertise to discuss the many key questions involved in this research—is this the appropriate vector for the disease, should a temporary vector be used to try to cure a long-term disease if it cannot be administered more than once, is the trial proposing to study the appropriate patient population, will the patient population have the appropriate genetic background, does the trial propose to study the appropriate stage of disease. These questions go beyond the safety of the vector, how to prepare it, and how to deliver it.

The RAC is safeguarding the field because RAC members work in and care about the field. The RAC has a responsibility to protect the gene transfer field so the first success finally is realized and so eventually gene transfer becomes an established clinical therapeutic field and not just a clinical research field.

The RAC will have dialogue about this issue and it will be put it on the RAC agenda. Stakeholders in this discussion will include patient advocates, representatives from IBCs and IRBs, and additional FDA representatives. The result of that discussion should be information about how RAC reviews are used, what is and what is not useful about the RAC review process, and recommendations about future direction.

XII. Closing Remarks and Adjournment

Dr. Fong thanked the RAC members and the OBA staff and adjourned the March 2012 RAC meeting at 3:15 p.m. on March 8, 2012.

[Note: Actions approved by the RAC are considered recommendations to the NIH Director; therefore, they 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: _____

Yuman Fong, M.D.
Chair
Recombinant DNA Advisory Committee

Attachment I: RAC Roster
Recombinant DNA Advisory Committee

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FAYL, Gilbert, Ph.D.
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Attachment II Public Attendees

[This list includes individuals who are not identified elsewhere.]

Xandra Breakefield, Massachusetts General Hospital
Ray Chow, Medgenics
C.L. Dellio, Medgenics
Mary Enama, NIAID
Ilan Irony, FDA
Nancy Jones, NIAID
Jocelyn Kaiser, *Science Magazine*
Sadik Kassim, National Cancer Institute, NIH (NCI)
Karen Kozarsky, ReGenX
Barbara Matthews, BioDirect
Maritja McIntyre, ReGenX
Andrew Miller, BCG
Richard Morgan, NCI
Amber Salzman, Alophera
Niv Shapir, Medgenics
Sonia Skarlatos, National Heart, Lung, and Blood Institute, NIH
Jim Wilson, University of Pennsylvania Medical Center
Rachel Witten, FDA

(plus one other individual whose name was not readable on the sign-in sheets)

Attachment III Abbreviations and Acronyms

AAV	adeno-associated virus
ASGCT	American Society of Gene and Cell Therapy
CAD	coronary artery disease
CKD	chronic kidney disease
CTLs	cytotoxic T cells
DSMB	data and safety monitoring board
eIF5AL1	eukaryotic translation initiation factor 5A-like 1
EPO	erythropoietin
ESA	erythropoiesis-stimulating agent
ESGCT	European Society of Cell and Gene Therapy
ESRD	endstage renal disease
FDA	Food and Drug Administration, U.S. Department of Health and Human Services
FH	familial hypercholesterolemia
GTSAB	Gene Transfer Safety Assessment Board
GVHD	graft-versus-host disease
GVL	graft-versus-leukemia
HDAd	helper-dependent adenovirus
HLA	human leukocyte antigen
hoFH	homozygous patients with FH
HSCT	hematopoietic stem cell transplant
IBC	institutional biosafety committee
iCasp9	inducible caspase 9
IRB	institutional review board
LDLR	LDL receptor
LINCL	late infantile neuronal ceroid lipofuscinosis
M6P	mannose-6 phosphate
MHC	major histocompatibility complex
NIAID	National Institute of Allergy and Infectious Diseases, NIH
NIH	National Institutes of Health
<i>NIH Guidelines</i>	<i>NIH Guidelines for Research Involving Recombinant DNA Molecules</i>
NSGCT	The Netherlands Society for Gene and Cell Therapy
OBA	Office of Biotechnology Activities, NIH
OD	Office of the Director, NIH
PBMCs	peripheral blood mononuclear cells
pu	particle units
RAC	Recombinant DNA Advisory Committee
RCA	replication-competent adenovirus
rHuEPO	recombinant human erythropoietin
SAEs	serious adverse events
siRNA	silencing RNA
TILs	tumor-infiltrating lymphocytes
VEGF	vascular endothelial growth factor
vp	viral particles
VRC	Vaccine Research Center, NIAID, NIH