RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

March 11-12, 2008

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

Contents

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

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

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The Recombinant DNA Advisory Committee (RAC) was convened for its 111th meeting at 8:00 a.m. on March 11, 2008, at the National Institutes of Health (NIH), Building 31-C, Conference Room 6, Bethesda, Maryland. RAC member Dr. David Williams (Acting Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 8:00 a.m. until 4:30 p.m. on March 11 and from 8:15 a.m. until 1:15 p.m. on March 12. The following individuals were present for all or part of the March 2008 RAC meeting.

Committee Members

Steven M. Albelda, University of Pennsylvania
Jeffrey S. Bartlett, Columbus Children's Hospital
Hildegund C.J. Ertl, The Wistar Institute
Hung Y. Fan, University of California, Irvine
Jane Flint, Princeton University
Ellen E. Grant, HealthNow New York Inc.
Jeffrey P. Kahn, University of Minnesota
Joseph Kanabrocki, The University of Chicago
Louis V. Kirchhoff, University of Iowa
Eric D. Kodish, The Cleveland Clinic Foundation
Prediman K. Shah, Cedars-Sinai Medical Center *(via teleconference)*
Robyn S. Shapiro, Medical College of Wisconsin
Nikunj V. Somia, University of Minnesota, Twin Cities
Scott E. Strome, University of Maryland
David J. Weber, The University of North Carolina at Chapel Hill
David A. Williams, Children's Hospital Boston/Harvard Medical School
John A. Zaia, City of Hope National Medical Center

RAC Executive Secretary

Jacqueline Corrigan-Curay, RAC Executive Secretary, Office of Biotechnology Activities (OBA), Office of the Director (OD), NIH

***Ad Hoc* Reviewers and Speakers**

Fabio Candotti, M.D., National Human Genome Research Institute, NIH
Harry L. Malech, M.D., National Institute of Allergy and Infectious Diseases (NIAID), NIH
Brian R. Murphy, M.D., NIAID, NIH
Naomi Rosenberg, Ph.D., Tufts University
Brian P. Sorrentino, M.D., St. Jude Children's Research Hospital
Adrian J. Thrasher, M.D., Ph.D., University College London *(via teleconference)*

Nonvoting Agency Representatives

Kristina C. Borror, U.S. Department of Health and Human Services (DHHS)
Daniel M. Takefman, U.S. Food and Drug Administration (FDA), DHHS

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

NIH Staff Members

Sandra Bridges, NIAID
Suk See Deravin, NIAID
Linda Gargiulo, OD
Mary Groesch, OD
Katherine Harris, OD
Robert Jambou, OD
Mary Joyce, National Heart, Lung, and Blood Institute (NHLBI)
Elizabeth Kang, NIAID
Laurie Lewallen, OD
Maureen Montgomery, OD
Marina O'Reilly, OD
Gene Rosenthal, OD
Tom Shih, OD
Sonia I. Skarlatos, NHLBI
Carolyn A. Wilson, FDA

Others

There were 82 attendees at this 2-day RAC meeting.

Attachments

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

I. Day 1 Call to Order and Opening Remarks/Dr. Williams

Dr. Williams, RAC Acting Chair, called the meeting to order at 8:00 a.m. on March 11, 2008. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (*NIH Guidelines*) was published in the *Federal Register* on February 13, 2008 (73 FR 8332). Issues addressed by the RAC at this meeting included a report from the Gene Transfer Safety Assessment Board (a subcommittee of the RAC), public review and discussion of four protocols, presentation and discussion of new developments and implications of insertional mutagenesis in X-linked severe combined immunodeficiency (X-SCID) gene transfer, discussion of proposed changes to the *NIH Guidelines* to address the biosafety considerations for synthetic biology, and discussion of immunotherapy for human papillomavirus (HPV) with regard to Appendix M-VI-A of the *NIH Guidelines*.

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 questions be addressed to the OBA committee management officer.

II. Minutes of the December 3-5, 2007, RAC Meeting/Drs. Fan and Grant

Dr. Grant noted that a few corrections had been made to the minutes of the December 3-5, 2007, RAC meeting.

A. Committee Motion 1

No formal motion was made, but the RAC voted unanimously, by voice vote, to approve the December 3-5, 2007, RAC meeting minutes. The vote was 14 in favor, 0 opposed, 0 abstentions, and 0 recusals.

III. Discussion of Human Gene Transfer Protocol #0801-896: A Phase I, Open-Label, Nonrandomized, Dose-Escalation, Multicenter Study to Assess the Safety and Cardiovascular Effects of the Implantation of Autologous Skeletal Myoblasts Modified to Express the SDF-1 Protein (MyoCell™ SDF-1) via Multielectrode Percutaneous Transendocardial Catheter (MyoStar™) with Cardiac Navigation Guidance (NOGA™) in Congestive Heart Failure Patients with Postmyocardial Infarction(s) with Prior Placement of an Implantable Cardioverter Defibrillator (ICD)

Principal Investigator:	Carl J. Pepine, M.D., University of Florida
Additional Presenters:	Barry J. Byrne, M.D., Ph.D., University of Florida; Kristin Comella, M.S., Bioheart, Inc.; Mark Penn, M.D., Ph.D., The Cleveland Clinic *(via teleconference)*; Richard T. Spencer, J.D., M.B.A., Bioheart, Inc.
Sponsor:	Bioheart, Inc.
RAC Reviewers:	Drs. Ertl and Shah and Ms. Shapiro

Drs. Strome and Kodish recused themselves from consideration of this protocol due to a conflict of interest.

A. Protocol Summary

The MyoCell™ stromal cell-derived factor 1(SDF-1) product candidate is a proposed treatment for the management of progressive heart failure in individuals with damaged myocardial tissue resulting from prior myocardial infarction. This product candidate contains autologous myoblast cells that are transduced with an adenoviral (Ad) vector expressing the SDF-1 protein. By injecting MyoCell™ SDF-1 into damaged, akinetic areas of myocardium, these regions may become populated with contractile skeletal muscle-like tissue that may have the ability to recruit stem cells to repair any damaged regions, thereby possibly improving heart function. It is anticipated that MyoCell™ SDF-1 will be delivered directly into the myocardium of the hearts of individuals suffering from congestive heart failure via Bioheart Inc.'s MyoCath™ needle-injection catheter system. The product may be delivered with a temperature-sensitive hydrogel to increase its bioretention and the engraftment of the cells. Diluted contrast media will be used to improve visualization of the injections.

MyoCell™ SDF-1 consists of patient autologous skeletal myoblasts expanded *ex vivo*, which will be transfected with an Ad serotype 5 (Ad5) vector with a cytomegalovirus promoter for SDF-1 expression. The product candidate will be suspended in a commercially available organ transplant medium for injection into areas of damaged, akinetic myocardium. It is anticipated that MyoCell™ SDF-1 will be provided on a custom-made basis from an approximately 5- to 10-gram skeletal muscle biopsy usually taken from the individual's quadriceps muscle. Subsequently, myoblasts will be isolated and expanded from the biopsy (via a proprietary cell culturing process), then transfected with SDF-1, and harvested once a sufficient number of cells are produced. Harvest will be by trypsinization, cell collection, and repeated washing with the transport medium to ensure removal of any residual serum and vector from culturing.

Following the final resuspension in transport medium, release testing will be conducted and MyoCell™ SDF-1 will be packaged and labeled for return shipment to the patient's treating physician for implantation. The product candidate's sterility will be controlled by the aseptic production method, and the intravenous (IV) bag in which it will be delivered will be gamma-sterilized and filled under aseptic conditions. Following injection into damaged myocardium, the SDF-1-expressing myoblasts may populate the implanted area and generate elastic, contractile skeletal-muscle-like tissue that has been shown to have the ability to recruit stem cells.

B. Written Reviews by RAC Members

Ten RAC members voted for in-depth review and public discussion of the protocol. Key issues included the novel use of the gene (SDF-1) in the context of myocardial disease, evaluation of a novel delivery method, and the risks of administering an immunogenic Ad vector to the heart.

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

Dr. Ertl suggested that the investigators test preclinically, in an appropriate animal model with preexisting immunity to Ad5, whether myoblasts transduced *in vitro* with an Ad elicit a T-cell or B-cell response to the antigens and whether the transduced myoblasts would become targets for Ad-specific CD8+ T cells, thus harming an already weakened heart muscle. She requested additional information about which cells in addition to myoblasts and fibroblasts might be transduced and the expected biodistribution of nonmyoblast-transduced cells. Regarding the appendix to the protocol, Dr. Ertl noted that the investigators described a number of preclinical studies without showing the data from those studies and requested those data for seven such instances. She also suggested that the plans for autopsy in the event of participant death should be more comprehensive. Dr. Ertl stated concerns relative to the protocol about testing for immune responses to Ad, which she suggested should be carried out before and after dosing. She also suggested that serum or plasma and peripheral blood mononuclear cells should be banked to be available for additional tests in case of a serious adverse event (SAE). Noting that 6 of 70 research participants treated with a similar product had died, Dr. Ertl asked for a detailed description of those deaths and the autopsy results. She also asked for additional information about the type of assays the investigators will use to test for B-cell or T-cell responses to SDF.

Because Dr. Shah had not joined the meeting yet, Dr. Corrigan-Curay summarized the written comments he had submitted prior to the meeting. Dr. Shah requested clarification of the rationale for using SDF-1. He noted that no consideration was given to measuring immune response to Ad and requested that the investigators assess both baseline and postdelivery cell-mediated and humoral immune responses. Noting that prior human studies of skeletal myoblasts raised questions about arrhythmogenesis and sudden death, Dr. Shah asked the investigators to discuss the rationale for again using the same cell type. He also requested detailed preclinical data on the safety and efficacy of the proposed product.

Dr. Shah joined the meeting by teleconference and discussed his additional concerns, including the potential risk of fatal arrhythmias from this therapy as seen in the previous trials with skeletal myoblasts. The requirement of an ICD mitigated this risk to some extent. However, a recent study by Professor Menasche (Menasche, et. al., Circulation 2008;117:1189-1200) using skeletal myoblasts in patients with heart failure failed to show benefit of the myoblasts compared to placebo. Post-hoc analysis did suggest that the higher dose might improve left ventricular remodeling even though the ejection fraction did not change. These results raise a fundamental question as to whether the proposed form of cell therapy has a likelihood of achieving overwhelming benefit to justify the increased risk of transcatheter endocardial delivery of the tranduced skeletal myoblasts. While this trial attempts to build on the previous trial in which untransduced myoblasts were used, it is not clear that the preclinical data has shown that using this adenoviral vector, in the face of pre-existing immunity to adenovirus, will lead to enhanced efficacy over the untransduced skeletal myoblasts that have not shown efficacy in a placebo controlled trial.

Ms. Shapiro asked the investigators to justify their choice to evaluate a novel agent contemporaneously with a novel delivery system, noting that doing so might enhance risks and complicate evaluation of the resulting safety data. Within the “Risks and Possible Side Effects” section of the informed consent document, Ms. Shapiro stated that the investigators should more clearly describe the risk of the MyoStar™ needle passing through the heart wall, clarify the reasons for excluding pregnant and lactating women, further discuss the preclinical data, and discuss their evaluation of the risk of death for study participants. In the “Alternative Procedures” section, Ms. Shapiro noted that discussion focused on cell-based therapies without addressing alternative therapies for treatment of heart failure in proposed participants. In addition, she requested information about the principal investigator’s (PI) financial relationship to Bioheart, Inc., in the “Source of Funding” section of the informed consent document.

C. RAC Discussion

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

- Dr. Zaia noted the possible impracticality of using a more extended dosing schedule within the first cohort of these very sick participants. He suggested that decisions about the timing of doses and how to stage the enrollment of new participants be left up to the local review committees.

- Ms. Shapiro and Dr. Zaia requested more information about the conflict of interest regarding The Cleveland Clinic, which is proposed as one of the sites for this clinical trial.

- Dr. Williams noted that the proposed reason for using genetically modified cells expressing SDF-1 is for mobilization of a stem cell that then leads to a regenerative phenotype. He asked whether, in the preclinical studies with this Ad, the investigators had documented mobilization of stem cells in animals. Dr. Williams also asked whether the investigators plan to look for mobilization of CD34+ cells in humans during the proposed clinical trial.

- Dr. Zaia summarized the request of several RAC members that the investigators provide preclinical evidence showing that, in the presence of Ad immunity, SDF-1 is still expressed and that no inflammation occurs in the myocardium of the mouse.

- Dr. Flint asked whether preclinical data would be provided to potential participants before they enroll in this trial.

D. Investigator Response

1. Written Responses to RAC Reviews

Regarding the rationale for SDF-1 transduction, the investigations noted that recent studies have demonstrated a natural but clinically inefficient stem-cell-based repair process that attempts to repair the heart following myocardial infarction. The effects of SDF-1 suggest that the delivery of skeletal myoblast (SKMB) that re-establishes SDF-1 expression in the hearts of patients with congestive heart failure (CHF) will lead to greater improvement in cardiac function than SKMB alone. In addition, a preclinical study conducted by some of the investigators' collaborators demonstrated that myoblast-based delivery of therapeutic proteins leads to an improved treatment effect compared with direct Ad injection, and suggested that already developed Ad vectors that encode secreted factors could potentially offer greater efficacy in combination with SKMB transplantation.

The sponsor agreed to add testing for immune responses to the protocol. This testing will be carried out prior to and after dosing to assess the titer of preexisting antibodies. In addition, T-cell responses to the vectors will be assessed before and after vector administration. The specific assays for these analyses are yet to be determined.

Despite early concerns regarding an apparent increase in arrhythmogenicity with myoblast transplantation from small-scale Phase I clinical studies, the investigators explained that recent larger scale Phase II clinical studies have shown no increased risk for arrhythmia with myoblast treatment, thus reinforcing its promise as a clinical therapeutic for CHF and ischemic cardiomyopathy. Myoblasts also survive and engraft within scar tissue better than any other cell type, making these cells the best platform for providing sustainable SDF-1 release in the heart. To date, Bioheart, Inc., has treated 75 class II and class III heart failure patients with myoblast transplantation and recently reported the early results of a 20-participant, multicenter, Phase I study of autologous myoblasts as the sole intervention in participants with CHF. This study indicated that catheter-based delivery of autologous myoblasts is feasible and safe in patients with chronic systolic left ventricular dysfunction. At 3 to 12 months, the incidence of adverse clinical events, including ventricular arrhythmias is not above that expected in individuals with class II or class III CHF,

and more than 83 percent of myoblast-treated research participants exhibited improvement in quality of life, heart failure class, or 6-minute walk.

Regarding the simultaneous evaluation of a novel agent and a novel delivery system, the investigators explained that they will be using the NOGA™ cardiac mapping system (Biosense Webster, Inc.) with the MyoStar® needle-injection catheter (Cordis Corporation) for delivery of the investigational biologic in this study. The NOGA™ is the most widely used and accurate delivery vehicle currently available, providing real-time three-dimensional mapping of patients' left ventricle prior to and during delivery of the biologic. Reproducible results with adequate safety profiles have been produced preclinically and clinically. The only alternative to percutaneous delivery via needle-injection catheter requires open-chest, full thoracotomy—a highly invasive procedure that would be more difficult for research participants to tolerate.

The risk of the MyoStar® needle perforating the heart wall during the experimental procedure is less than 1 percent, based on all clinical cases reported to date. All physicians using the MyoStar® catheter for injection must successfully complete a 2-day training course in live animals at a Johnson & Johnson training facility, to ensure that all physicians using the system are well versed with the catheter and have had the opportunity to use it *in vivo* prior to clinical use.

The risk of death cannot be eliminated in this proposed study. The patient population eligible to participate in this study suffers from CHF and, therefore, is already at substantial risk for potentially lethal cardiac events such as uncontrollable ventricular arrhythmia. Based on the available preclinical and clinical data, the investigators and the sponsor believe that participants will not be subjected to a higher risk of death by receiving the investigational product. However, the interventional procedure itself, as well as the angiogenesis and myogenesis that are believed to follow delivery of the investigational product, introduce variables that may change (adversely or positively) the participant's health.

The use of autologous myoblasts in the heart has been studied extensively during the past 20 years and has not been shown to elicit an immune response, as the cells are recognized as self. The direct injection of an Ad vector to transfect cells *in vivo* has been analyzed in preclinical and clinical studies. A meta-analysis of the multinational Phase IIb/3 trials AGENT-3 and AGENT-4 in participants with angina revealed no safety concerns; the participants in these trials received up to $1x10^{10}$ viral particles. The proposed procedure for the current trial is perceived to be a safer method: The number of viral particles is much lower and the investigators intend to transfect the cells *ex vivo* and wash them thoroughly to remove all Ad particles prior to implantation.

Myoblasts will make up greater than 90% of the injected cell population; however, the population will also include fibroblasts (2nd highest by percentage), myotubes, myofibers, and stem cells. These cell types account for greater than 99% of the population. Most of the cells that are injected into the heart via an intramyocardial delivery catheter end up in the lungs and later in the heart, kidneys, and liver. A similar biodistribution pattern occurs for most cell types delivered in this manner and has been deemed acceptable by many regulatory bodies, including the FDA.

The investigators agreed to conduct an *in vitro* experiment to determine the percentages of virus in the cells and on the cells. Based on the investigators' preclinical data to date, it does not appear that the low level of surface-bound Ad5 has significant biological or adverse effects.

2. Responses to RAC Discussion Questions

Dr. Pepine explained some of the previous human studies. Several hundred patients were studied, and the results were well documented in published literature using Ad-derived vectors for delivery of a variety of gene therapies. Dr. Pepine and colleagues participated in two of those studies, which were completed several years ago. No evidence in the literature suggests that the Ad vector given in a two-log higher dose caused any problems with myocarditis or any other cardiac problems. The therapies used Ad with a vascular endothelial growth factor vector as well as a basic fibroblast vector.

In response to concerns expressed by Dr. Ertl and other RAC members about the death of 6 of 75 research participants treated with a similar product in several Bioheart, Inc., trials, Dr. Pepine explained that patients with CHF of this magnitude have a 3-year mortality rate of 35 percent to 40 percent. About half of those deaths are arrhythmic deaths, and studies have shown that inserting an internal defibrillator prolongs life but does not eliminate the arrhythmic or other deaths. The deaths in question could be due to either the experiment or the natural course of CHF or other causes. Given that about 200 patients have been treated with myoblasts thus far, the death rate would be anticipated to be substantially higher than that reported in the literature if there were a serious safety signal from the SKMBs. In a period of 6 to 12 months the normal mortality rate in those studies is 10 percent to 20 percent; 6 deaths of 75 participants is slightly less than 10 percent. Dr. Pepine acknowledged—and a data and safety monitoring board (DSMB) agreed—that there is no way to know the cause of those deaths other than to ascribe them to a subgroup that has a high mortality. All of the six participants who died had a history of prior documented ventricular tachycardia or ventricular fibrillation; such individuals are specifically excluded in the current protocol. In addition, none of the participants who died were on prophylactic antiarrhythmic agents, whereas the current protocol calls for use of prophylactic agents if there is a prior history of arrhythmia.

At the suggestion of Dr. Ertl, Dr. Pepine agreed that the protocol should dose participant 1 and then wait 3 or 4 weeks; dose participant 2 and wait another 3 or 4 weeks; dose participants 3, 4, and 5, assuming no SAEs such as arrhythmia are encountered after the waiting period for participants 1 and 2; wait 30 days after cohort 1 (participants 1 through 5) and after the medical monitor conducts a thorough review of all events; and then begin dosing the next cohort.

Regarding the concern expressed by Ms. Shapiro and Dr. Zaia about a conflict of interest at The Cleveland Clinic, Dr. Pepine explained that a surrogate investigator would be appointed there, which will remove Dr. Penn's potential conflict of interest. The conflict of interest committee at The Cleveland Clinic has approved a full conflict management plan. Patients of Dr. Penn who are interested in this trial must be approved by other physicians to be included in this trial; Dr. Penn will not conduct any of the procedures, and there will be independent review of any data coming from Dr. Penn's laboratory.

In response to Dr. Williams' question about mobilization of CD34+ stem cells, Dr. Byrne responded that the preclinical studies have not been conducted with marked marrow, which would be the only way to reliably determine which cell population is migrating; similar studies have been conducted in other sites (e.g., the cornea). The human studies are not expected to be able to detect this rare cell population, and the loss of the markers in myocardium would be difficult to detect in humans. Therefore, no biopsies of these participants are planned. The low level and local expression of SDF-1 do not increase remote expression but increases capture of the cells. Dr. Pepine explained further that the investigators have not seen any increase in circulating SDF-1 levels nor have they seen any change in circulating CD34+ cells with SDF-1-expressing SKMBs in the rat ischemic myopathy model.

E. Public Comment

Dr. Borror noted that the informed consent document contains complex language. She suggested that an explanation of "genetically modified" cells be added and noted that the differences between "MyoStar™" and "MyoCell™" might be confusing.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

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

Preclinical Issues

- At a minimum, additional preclinical studies are needed to determine whether the transduced myoblasts elicit a T-cell or B-cell response to Ad antigens. If they do, the cells could become the target of Ad-specific CD8+ T cells, leading to their destruction, which could cause additional injury

to an already weakened heart muscle. An animal model of heart failure induced through myocardial ischemic injury could be used to test whether Ad specific CD8+ T cells are detectable and, if so, whether they affect either the safety or the efficacy of the transduced myoblasts. Since Ad5 does not replicate in rodents, the animal model needs to be adapted to best mimic the immune response in humans to Ad5. It is also crucial that safety and efficacy studies are carried out in animals with preexisting immunity (especially specific CD8+ T cells) to Ad5 since such immunity is expected in human research participants.

- No preclinical data measuring CD34+ or CD34+ derived cells at the injection site were provided. These data are important and should be submitted.

Clinical/Trial Design Issues

When the appropriate preclinical data have been obtained, the following should be considered for the clinical trial design.

- In Bioheart's previous trials with intramyocardial injection of myoblasts, four deaths occurred in the first 3 weeks after dosing. As an additional safety precaution, a waiting period of 3 to 4 weeks should be added between the first three participants in each cohort. This would be in addition to the waiting period of at least 30 days between cohorts.

- An increase in the incidence of arrhythmia among participants should be considered a stopping rule or at the least as a trigger for DSMB review.

- To be able to detect whether the vector is causing immune reactions, participants should be tested for preexisting immunity to Ad, and CD8+ T-cell responses should be measured.

- Autopsies should not be limited to the heart.

Ethical/Legal/Social Issues

- The informed consent document should be revised to reflect the findings of additional preclinical data, presuming these data support moving into a clinical trial. In addition, the fact that an ICD does not eliminate the risk of a fatal arrhythmia needs to be stated explicitly. Finally, although this is a Phase I study and benefits to the participants are not expected, the findings from the Menasche *et al.* study should be included in discussing the rationale for using SKMBs in this population.

G. Committee Motion 2

Dr. Williams summarized the comments and concerns of the RAC to be included in a letter to the investigators and the sponsor. Dr. Williams asked the RAC to approve these summarized recommendations; no official motion was made or seconded. The vote was 12 in favor, 0 opposed, 0 abstentions, and 2 recusals.

IV. Discussion of Insertional Mutagenesis in X-SCID Gene Transfer: New Developments and Implications for Future Trials

RAC Moderators:	Drs. Kodish and Somia
Speakers:	Fabio Candotti, M.D., National Human Genome Research Institute, NIH; Harry L. Malech, M.D., NIAID, NIH; Brian P. Sorrentino, M.D., St. Jude Children's Research Hospital; Adrian J. Thrasher, Ph.D., M.D., University College London *(via teleconference)*

Dr. Williams recused himself from consideration of this discussion due to conflicts of interest.

A. Introduction/Dr. Somia

In response to the report of a T cell leukemia in a research participant in the British X-SCID trial, Dr. Somia explained that the RAC was being asked to review the recommendations the committee had developed following discussions of four similar adverse events (AE) due to vector induced insertional mutagenesis in the French X-SCID trial. Dr. Somia provided an introduction to the topic by presenting a summary of retroviral and lentiviral vectors, trends in retroviral vector usage in clinical trials from 1988 through 2007, and the RAC's recommendations from previous RAC meetings on X-SCID gene transfer.

B. U.K. Trial Update/Dr. Thrasher

Dr. Thrasher discussed the SAE and the molecular characterization in the U.K. trial to date. CD34+ cells were transduced with a gamma retroviral vector expressing gamma C and infused into 10 children in this study. All research participants gained substantial therapeutic effect, with the majority showing normalized lymphocyte numbers and function as well as good reconstitution of humoral immunity. Two years after receiving the transduced cells, Participant 8 showed the typical features of acute lymphoblastic leukemia (ALL), including splenomegaly and bruising. The research participant remains in remission 3 months after treatment and is doing well, with no evidence of residual disease.

Molecular analysis of the cells showed vector insertion 35 kb upstream of the oncoprotein LMO2 and other mutations in Notch1 and deletion of the alternative reading frame (ARF) tumor suppressor locus that may also have contributed to the leukemia. In the French trial, which used a similar vector, four participants developed T-cell ALL, and three of those participants had insertions in and around the LMO2 locus. Three of the participants responded well to chemotherapy and remain in remission; however, the fourth participant died.

The U.K. trial was finished before this SAE arose; no vector stocks remain, and the investigators do not intend to use this vector to treat additional individuals. The investigators have developed a self-inactivating gamma retroviral vector-encoding gamma C, with an internal promoter, elongation Factor 1 alpha. The vector has been tested in several animal models and has been shown to correct defects efficiently in mice. It has also been shown via surrogate mutagenicity assays to be significantly less mutagenic, with mutagenicity undetectable in the model systems currently in use. This vector is currently in production, and a clinical trial is planned for later this year.

C. Risk for Insertional Mutagenesis/Dr. Sorrentino

Dr. Sorrentino discussed whether the risk for insertional mutagenesis is uniquely elevated in X-SCID and whether lentiviral vectors are a less oncogenic alternative for use in clinical trials. On the basis of data from several animal studies, Dr. Sorrentino concluded that the risk is elevated in X-SCID. Specific genetic alterations are associated with X-SCID T-cell leukemia, including LMO2 activation and the loss of function of the ARF tumor suppressor. Because specific genetics are involved in this disease and as new vectors are designed, animal models will need to represent the appropriate genetics.

Dr. Sorrentino and colleagues have developed a model using mice that have the X-SCID phenotype due to a gamma C gene deletion, and that are sensitized due to the loss of ARF. Cells are then transplanted after being transduced with various vectors and tumor development is studied. This model recapitulates the T-cell malignancies seen in X-SCID patients; in two independent experiments, about 85 percent of the animals at 1 year have T-cell lymphoma. These tumors show mature differentiation markers that are quite similar to those in X-SCID leukemia patients. However, the human experience is not completely replicated in this model because no LMO2 insertions have been seen to date. It is presently unknown to what degree adenosine deaminase-deficient SCID (ADA-SCID) will be similar to or different from X-SCID with regard to risk, but LMO2 insertions were detected in an ADA-SCID clinical trial.

Regarding the use of lentiviral vectors, Dr. Sorrentino noted that lentiviruses have a different integration pattern not associated with the oncogenes know to have caused problems with retroviral vector insertion.

SIN vectors lacking viral transcriptional regulatory regions and enhancers can more easily be generated in lentiviruses compared to with retroviruses. He concluded that safety can be improved by eliminating viral enhancers and using appropriate cellular promoters; insulators also may decrease the risk of insertional mutagenesis, although their effect is not absolute in lymphoid cells. It is not clear how the safety profile of SIN lentiviral vectors will compare with that of SIN gamma retroviral vectors. He noted that researchers are developing and testing important new vector designs for efficacy and safety in appropriate animal models.

D. ADA-SCID/Dr. Candotti

Dr. Candotti discussed his experience with ADA-SCID. ADA disease, constituting 16 percent of SCID cases, is the second most common cause of SCID. ADA deficiency is a metabolic disease that affects the immune system as well as other organs and systems such as the skeletal system, the gastrointestinal (GI) tract, the endocrine system, and the central nervous system; the ADA enzyme is ubiquitous, and therefore, its lack of expression strains all the organs and systems that use it. The lack of the ADA enzyme results in the accumulation of deoxymetabolites toxic to lymphoid cells. Some ADA enzyme activity is preserved in some cases, resulting in a less severe presentation and milder versions of the disease.

More effective therapies for ADA-SCID are needed because the results of bone marrow transplantation are less than optimal. If patients have human leukocyte antigen (HLA) identical sibling donors, the survival after allogeneic bone marrow transplantation is acceptably high; however, only 25 percent or less of patients have that ideal donor. Transplantation from a parent donor results in a dismal survival rate. ADA-SCID can be treated with enzyme replacement therapy. A bovine version of ADA is available; it can be purified and pegylated, which increases its half life and reduces its immunogenicity. This therapy has been used extensively in patients because of the poor results of transplant, but it is not a cumulative therapy. It is only effective to some extent in four out of five patients, and most patients continue to require the use of immunoglobulins. Because the protein is a bovine protein, as the immune system of the patient improves, it recognizes this protein as foreign and produces an immune reaction against it that, in some patients, leads to the development of neutralizing antibodies, which becomes a significant management problem. This therapy has a 74-percent survival rate, so this therapy is not effective for approximately 25 percent of patients.

Clinical trials for the treatment of ADA-SCID using gene transfer have been conducted for many years. Recently clinical benefits have been achieved in an Italian trial in which the participants were not also being treated with PEG-ADA and were administered busulfan to increase the selective advantage of the transduced cells. Long term marking and clinical benefits were observed in several subsequent trials without any SAEs similar to those in the X-SCID trials.

The vector insertions were determined in some of the ADA SCID studies and compared to those in the X-SCID studies. Preferential integration was observed near transcriptional start sites, gene dense regions and highly expressed genes. Integrations have been detected near oncogenes; however, neither over-expression of those genes nor accumulation of clones has been observed. The integration patterns were similar in ADA and X-SCID gene transfer; however, the outcomes differed. Perhaps the function of the transgene is involved. Gamma C is a proliferation factor. There may be different cooperation partners for the two gene products. Although technical differences exist in the gene transfer protocols related to ADA-SCID compared with X-SCID, those differences do not explain the absence of leukemia in ADA trials.

For future trials, Dr. Candotti suggested that alternative viruses be considered, for example, vectors derived from lentiviruses, a foamy virus, or avian sarcoma and leukosis virus.

E. NIH Clinical Trial for X-SCID/Dr. Malech

Dr. Malech provided a brief review of the NIH clinical trial of gene transfer for X-SCID in older children as a salvage treatment. He cited examples of the problems affecting a subset of older children with X-SCID who have poor engraftment and/or waning immunity in the 10 years following their haploidentical T-cell

depleted transplant in infancy. Medical issues include alopecia and skin rashes, *Molluscum contagiosum*, warts, bronchiectasis and recurrent pneumonias, loss of alveolar and bronchial function, and significant reductions in normal weight and height.

Dr. Malech summarized the protocol, which uses a similar vector to those used in the French and British trials, the outcome for all three participants, discussed treatment alternatives (matched unrelated donor or cord blood transplants), and discussed proposed protocol modifications that have been enacted for the older children. He noted that age appears to matter, in that older children with X-SCID who are treated with gene transfer do not demonstrate the vigorous *in vivo* expansion of gene-marked T cells observed in X-SCID infants. Possible factors for this age difference include poor thymic function, poor marrow engraftment, and blocking of expansion by the presence of resident donor T cells. The proposed conditioning regimen for the NIH protocol is to administer keratinocyte growth factor before and after conditioning and then administering fludarabine followed by busulfan followed by infusion of the gene-corrected cells. Although this proposal has been approved, no research participants have yet been treated.

Regarding the next generation of gene transfer for X-SCID, Dr. Malech stated the need to develop vectors that reduce the targeting of transcriptional start sites, such as lentivectors. SIN vectors also need to be developed, insulators should be incorporated, and mammalian promoters should be used. New X-SCID vectors should be tested extensively for oncogenic potential using the informative mouse systems, and the efficacy and safety of these new vectors also should be tested for safety and efficacy in a large-animal model such as the X-SCID dog that closely models human X-SCID.

Dr. Malech briefly discussed the SAEs recently noted in two research participants in a gene transfer study for X-linked chronic granulomatous disease although it is unknown whether these events are relevant to the discussion of X-SCID or ADA-SCID. In the German study, a retroviral vector expressing SF71-gp91^{phox} was used to transduce CD34+ cells resulting in high levels of gene marking in neutrophils. There was a profound *in vivo* clonal outgrowth of those myeloid clones where vector had inserted in and activated MDS1-EVI1, PRDM16 or SETBP1. The dominant gene marked clones with inserts in MDS1-EVI1 in each patient exhibited monosomy7. One participant died of infection at 2 years, having lost oxidase activity despite high-level gene marking, and the second participant continues to have high-level gene marking but also has lost oxidase activity. The safety of the spleen focus-forming virus-based vector used in the Frankfurt study has been called into question, although other unknown factors might have been responsible for the AEs seen in that trial.

F. Ethical Implications/Dr. Kodish

Dr. Kodish discussed ethical implications, including research vs. clinical ethics, risk-benefit assessments, clinical equipoise, and issues related to assent. Research ethics involves a calculation of risks to the research participant; benefits to the participant, to society, and/or to investigators or sponsors; and available alternative treatments. Code of Federal Regulations 45, Part 46 Protection of Human Subjects, Subpart D mandates additional protections for children, who are considered vulnerable research participants, by requiring more focus on benefits to the participant rather than benefits to others.

Equipoise involves the absence of consensus within the expert medical community regarding the comparative merits of the intervention to be tested. If equipoise is disturbed, a study should be stopped. Conventionally, equipoise is considered within a randomized controlled trial as being within a study, for example, arm A compared with arm B. The more relevant notion of external equipoise asks whether a particular investigational approach is as good as the approach in other trials.

The regulatory definition of assent is a child's affirmative agreement to participate in research; mere failure to object should not be construed as assent. Child research participants who are old enough to participate in the decision and, in the case of young people with SCID whose quality of life is impaired profoundly, should have a major voice in these decisions.

G. RAC Discussion

Dr. Kodish explained that the RAC would now revisit its recommendations on using gene transfer for X-SCID, given the new case of leukemia seen in the London trial. In March 2007, the RAC had recommended:

- Retroviral gene transfer studies for X-linked SCID should be reviewed, on a case-by-case basis, and limited, pending further data, to patients who have failed identical or haploidentical stem-cell transplantation or for whom no suitable stem cell donor can be identified. Case-by-case review would include appropriate risk:benefit analysis accompanied by implementation of appropriate informed consent and monitoring plans.

- There are not sufficient data or reports of adverse events directly attributable to the use of retroviral vectors at this time to warrant cessation of other retroviral human gene transfer studies, including studies for non-X-linked SCID. Such studies may be justified contingent upon appropriate risk:benefit analysis accompanied by implementation of appropriate informed consent and monitoring plans.

The RAC discussed the March 2007 SCID trial recommendations, which were originally formulated in 2005 and revisited but not changed in 2007. Comments made by RAC members included the following: The gene transfer field will move forward with safer vectors, but the ultimate testing of safety will have to occur in humans; determination of SCID trial safety and appropriateness should be made on a case-by-case basis; and the RAC should encourage the exploration of newer generation vectors.

Dr. Malech explained the consensus in the medical community—if a child with SCID has a fully matched sibling, a transplant from that sibling is the treatment of choice. Such treatment is low risk, and the short-term and long-term outcomes are positive. Dr. Sorrentino added his view that, for SCID patients older than 3 months of age and without a matched sibling, gene therapy and haploidentical transplantation are considered equivalent experimental therapies, with different risks and benefits but with similar risk-benefit ratios.

Dr. Takefman stated that the FDA recommendations are similar to the RAC recommendations; a minor difference is that the FDA recognizes that some patients would not be good candidates for a haploidentical transplant if they have existing infections. Carolyn A. Wilson, Ph.D., FDA, clarified that the FDA would allow use of gene transfer if X-SCID child-patients presented with many underlying infectious complications, thus making them not good candidates for haploidentical or identical transplants. Dr. Takefman added that the FDA would need to be presented with convincing preclinical data to change its recommendation.

Regarding vector safety, Dr. Takefman explained that the FDA (specifically, Dr. Wilson) has been working with the DHHS National Toxicology Program to conduct a large-scale animal study to look at Moloney vectors vs. human immunodeficiency virus (HIV) vectors and SIN vectors vs. non-SIN vectors. Data from this study will be available this summer.

H. Committee Motion 3

It was moved by Dr. Ertl and seconded by Dr. Fan that the two RAC recommendations from 2005 and 2007 remain as they were written. The RAC also encouraged the exploration of new vectors with the goal of reducing the risk of insertional mutagenesis. The vote was 12 in favor, 0 opposed, 0 abstentions, and 0 recusals.

[At this point in the meeting, Dr. Kodish assumed the duties of Acting RAC Chair.]

V. Discussion of Human Gene Transfer Protocol # 0801-895: A Phase I Study of Gene Transfer for Patients with Fanconi Anemia Complementation Group A (FANCA)

Principal Investigator:	Pamela S. Becker, M.D., Ph.D., University of Washington
Additional Presenters:	Erica C. Jonlin, Ph.D., University of Washington School of Medicine; Hans-Peter Kiem, M.D., Fred Hutchinson Cancer Research Center and University of Washington
RAC Reviewers:	Drs. Kodish and Williams
Ad hoc Reviewer:	Naomi Rosenberg, Ph.D., Tufts University

Drs. Kahn, Somia, Strome, and Zaia recused themselves from consideration of this protocol due to conflicts of interest. Dr. Corrigan-Curay stated that Dr. Williams was previously involved with a Fanconi anemia trial using a gamma retroviral vector that is now closed.

A. Protocol Summary

Fanconi anemia (FA) is a rare inherited blood disease characterized by congenital abnormalities, predisposition to cancer (including leukemia) much earlier in life than usual, and bone marrow failure leading to low blood counts (aplastic anemia), the latter being the major cause of illness and death. Transplantation of bone marrow or blood stem cells from unaffected donors is the only proven curative treatment for patients suffering from marrow failure. However, transplantation for patients with unrelated donors has been associated with significant complications and fatal outcome; this approach has been even less successful for these patients than for patients with a sibling donor whose immune system matches that of the patient. In addition, recent data suggest that graft-versus-host disease, a serious side effect of transplantation, increases the incidence of head and neck cancers.

Gene replacement therapy using autologous hematopoietic stem cells, which have been genetically modified with the Fanconi gene, is a potential alternative treatment, particularly since gene-corrected cells have a survival advantage. In addition, FA cells are highly sensitive to low doses of cyclophosphamide, which could be used to increase the proportion of genetically modified cells and also eliminate unmodified cells. Gene therapy for FA, however, has to date been limited by low gene transfer efficiency, resulting in no clinical benefit. Part of this problem has been the limitation of gammaretroviral vectors, which require cell division and extended cell culture time for efficient transduction. This is a particular problem for FA, since FA cells have an increased rate of apoptosis, and thus, their ability to divide and grow in culture is significantly reduced. Using mouse and large animal models, significant improvements in the transduction of hematopoietic stem cells have been made using lentiviral vectors. In contrast to gammaretroviral vectors, lentiviral vectors do not require cell division for transduction and can transduce stem cells even in very short transduction protocols. In normal dogs and non-human primates, CD34+ cells can be efficiently transduced with a short overnight transduction culture.

The objective of the study is to transfer the FA gene for complementation group A by lentiviral vector to autologous CD34+ cells from patients with FA, and reinfuse them into recipients pre-treated with cyclophosphamide, with the ultimate goal of curing the bone marrow disorder.

B. Written Reviews by RAC Members

Twelve RAC members voted for in-depth review and public discussion. Key issues included possible serious risks to the participants from the introduced transgene (FANCA), potential malignant transformation of CD34+ cells as a known risk of retroviral vectors, and the potential for development of monosomy 7 chromosomal abnormality, as recently reported in participants in a clinical trial in Germany that used a retroviral vector.

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

Dr. Kodish suggested changing the title of the well-written informed consent document from gene “therapy” to either gene “replacement” or gene “transfer.” Regarding the assent/consent process, he

asked for additional details about how information would be shared with potential child participants, particularly those between the ages of 9 and 12 years who might participate in the enrollment decision. Dr. Kodish asked the investigators to explain why some participants who might benefit from related stem-cell transplantation could be enrolled in this study and whether a participant in this study who did not show improved blood counts could be eligible for stem-cell transplantation subsequent to participation. He requested clarification of the need for using AMD 3100 in the apheresis/harvest procedure, since this drug has not yet been approved by the FDA and therefore poses a greater than minimal risk to participants. Dr. Kodish commended the investigators for their clear discussion of the issues surrounding long-term cancer risk and assessment in individuals with FANCA.

Dr. Williams expressed concern about exposing FA patients to nonablative deoxyribonucleic acid (DNA)-damaging agents. He asked about a "backup plan" if participants demonstrate prolonged and severe aplasia after exposure to cyclophosphamide, whether such individuals would be considered as candidates for allogeneic transplant, and whether ablative preconditioning would be used. Dr. Williams requested that the investigators provide evidence that the proposed clinical vector can efficiently transduce bone marrow or CD34+ cells from individuals with FA. He suggested that the investigators use a minimal collection target and/or a minimal transduced CD34+ population as a guideline for continuation into the infusion phase of the proposed protocol, thus reducing the risk to participants. Dr. Williams also expressed concern about the role of monosomy 7 and asked the investigators for data showing that the proposed lentiviral vector does not insert into oncogenes in FA CD34+-derived samples.

Ad hoc reviewer Dr. Rosenberg asked about the predicted survival of FA cells during the overnight incubation period and what the investigators consider the minimal number of cells required for transduction. She requested that the investigators comment further on the potential benefits of using a lentiviral vector compared with a gamma retroviral vector, particularly with regard to integration. Regarding the animal experiments, she asked how long the animals would be monitored for development of leukemia, and whether the FANCA-null mice were more susceptible to leukemogenesis than normal litter mates following infection with oncogenic gamma retroviruses. Noting that the investigators propose to use Southern blot analysis, Dr. Rosenberg asked for the rationale for not using a more sensitive and rigorous analysis to detect the transgene, in the event of the death of a participant.

C. RAC Discussion

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

- Dr. Williams pointed out that the mouse knockouts for FANCA are not considered human homologs because they do not develop aplastic anemia and do not develop carcinomas or any other cancer.

- Dr. Williams reiterated his significant concern about exposing these potential research participants (who are already aplastic) to DNA-damaging agents, which have a high risk of inducing leukemia in patients because of the proposed administration of a subablative dose. He explained his preference for one of two approaches: either leaving out cyclophosphamide altogether or giving ablative doses of cyclophosphamide and then depending on the transgene-transduced cells for reconstitution. The most conservative and safest approach for the participants is not for initial participants to use a DNA-damaging agent because preclinical efficacy data are not convincing and because of the increased potential risk of leukemia due to the survival of genetically unstable, non-transduced stem and progenitor cells that have DNA damage from cyclophosphamide exposure.

D. Investigator Response

1. Written Responses to RAC Reviews

The investigators provided a copy of the assent form that was prepared for potential participants who are 7 to 11 years old; the consent form will double as the assent form for children approximately 12 years of

age and older because it is written at the sixth-grade reading level. The information in the assent form will be shared with potential child-participants in the company of their parents/guardians. Because this is a gene transfer clinical trial, in addition to the pediatric Fanconi subinvestigator on the protocol, the PI also may attend the consent and assent conferences with the parents/guardians and the child.

Because the baseline risk of malignancy over 2 years for 15 participants is as high as 1 in 4, any malignancy reported as a SAE will need to be interpreted and assessed, and the investigators will obtain all tumor tissues for analysis for the transgene.

Because granulocyte-colony stimulating factor has been shown to be inadequate to mobilize peripheral blood stem cells for FA patients, the investigators in this trial propose to use AMD3100 (after the FDA approves it) for the mobilization indication; this approval is anticipated by the end of 2008. AMD3100 has been studied for stem-cell mobilization in patients who do not mobilize adequate stem cells as well as in normal donors, and in both groups it was successful and well tolerated.

The investigators agreed to exclude potential participants who have ever had abnormal cytogenetics associated with myelodysplastic syndrome, including monosomy 7, so as not to risk exposure to agents that might accelerate progression.

Regarding the exposure of FA patients to nonablative DNA-damaging agents, the investigators explained that the rationale for proposing to use cyclophosphamide is to create “space” in the marrow and promote engraftment of the gene-modified stem cells. Without preparation, there may not be engraftment of transduced cells, as was uncovered in another trial. Because of the concern regarding the potential for secondary leukemia, the investigators propose not to use cyclophosphamide prior to the infusion of gene-modified stem cells, at least for the initial participants. The Fanconi mice have been observed for 3 to 6 months, during which time they received repeated cyclophosphamide doses, and leukemia was not observed.

The backup plan should participants demonstrate prolonged and severe aplasia after exposure to cyclophosphamide is to proceed to allogeneic stem-cell transplantation from either an unrelated or a haploidentical donor. A suitable donor will be evaluated and worked up prior to each research participant’s enrollment in this trial.

Because it is difficult to obtain sufficient numbers of CD34+ cells, the investigators have been reluctant to assign a specific minimal collection cell number or a minimal transduced CD34+ population. Transduction efficiency with the lentivirus has been about 60 percent. The investigators are also studying the effect of hypoxia and the use of reducing agents during the transduction to preserve the hematopoietic progenitor cell numbers. They decided to propose a target cell number of 2 million CD34+ cells/kg, a number derived from the minimal number of cells needed to engraft for patients undergoing myeloablative transplant procedures for malignancies. Although results are generally better with 5 million CD34+ cells/kg, these numbers are unlikely to be achieved with FA patients, and the 2 million CD34+ cells/kg number is usually sufficient for blood-cell recovery in such patients.

In a study of the integration of murine leukemia virus-based and HIV-based vectors in a primate model, the investigators found no evidence of clonal expansion with any of the lentiviral vectors. The advantages of the lentiviral vector proposed for this trial—SIN design and a relatively weak internal “housekeeping” promoter—suggest an improved safety profile relative to gamma retroviral vectors.

In a dog experiment that achieved 1 to 2 transgene copies per cell, the animals have been monitored for leukemia for up to 3 years; no clonality has been observed for the canine or primate models with any of the lentiviral vectors.

Southern blots will be used to confirm the presence of integrated transgene. Quantitative real time PCR and LAM-PCR will also be performed.

2. Responses to RAC Discussion Questions

Dr. Becker acknowledged that the investigators did not show any data for cyclophosphamide preconditioning because those preclinical experiments are still in progress.

Dr. Kiem stated that the dose required to kill residual Fanconi cells is currently unknown. The proposed dose of 60 mg of cyclophosphamide, spread out at 15 mg for 4 days, is likely to be myeloablative in the allogeneic setting. However, the allogeneic setting will not allow rigorous testing of this hypothesis because of the allogeneic defect in the T cells that can eliminate the host population. To rigorously test a myeloablative effect, the investigators would have to conduct autologous studies with cyclophosphamide, which could not practically be accomplished in a human population—and the mice are not likely to be predictive for the relevant dosing and scheduling.

In response to strong concerns expressed by Dr. Williams, Dr. Kiem noted that the investigators had already eliminated the preinfusion cyclophosphamide and could agree to leave out the post-transplant cyclophosphamide dose as well. Later in the discussion, Dr. Kiem agreed not to use cyclophosphamide in this trial, at least for the initial several participants.

Dr. Becker explained that the investigators will make sure that an unrelated or haploidentical donor is available for each research participant, should that need arise. If an ablative consequence occurred, transplantation would be ready to proceed immediately.

E. Public Comment

Dr. Borror stated that the informed consent document contains complex language that should be simplified. Definitions of some complex terms—such as “genetically modified,” “venus catheter,” and “contaminate”—should be included in the document.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

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

Clinical/Trial Design Issues

- The use of cyclophosphamide, which can damage DNA, is a significant safety concern. In the treatment of pediatric cancers, cyclophosphamide has been associated with post-therapy development of secondary leukemias. FA patients are susceptible to DNA-damaging agents, have a cellular phenotype of genomic instability, and are also at increased risk of developing acute myeloid leukemia and other solid tumors. If the proposed dose of cyclophosphamide is nonablative, it may allow the continued presence of potential leukemia-prone noncorrected hematopoietic stem cells. Indeed, theoretically, treatment with nonmyeloablative doses of cyclophosphamide could further increase this risk by creating DNA damage and genomic instability in residual, noncorrected stem and progenitor cells that escape death. As such, the study design should be modified to eliminate the exposure of the research participants to pre-transfer and post-transfer gene therapy with DNA-damaging agents, and the study hypothesis should focus on determining whether engraftment can be obtained with the use of the lentiviral vector and briefer transduction methods.

- A suitable haploidentical or unrelated donor for allogeneic transplant should be identified prior to gene transfer, and all necessary steps should be taken to enable a transplant to occur immediately after gene transfer in case the research participant develops prolonged and severe aplasia. In the absence of exposure to DNA-damaging agents, having a suitable allogeneic donor immediately available may be less critical.

Ethical/Legal/Social Issues

- The assent document should be revised and simplified. As written, it makes the protocol sound like treatment, not research. In addition, all technical terms should be defined (e.g., genetically modified, venous catheter, hydration).

G. Committee Motion 4

Dr. Williams orally summarized the RAC recommendations. It was moved by Dr. Ertl and seconded by Dr. Flint that the RAC recommendations be included in the letter to the investigators as expressing the comments and concerns of the RAC. The vote was 10 in favor, 0 opposed, 0 abstentions, and 4 recusals.

VI. Proposed Changes to the *NIH Guidelines* to Address the Biosafety Considerations for Synthetic Biology

Presenters: Dr. Corrigan-Curay; Naomi Rosenberg, Ph.D., Tufts University;
Participants: Claudia A. Mickelson, Ph.D., Massachusetts Institute of Technology (*via teleconference*); Nicholas Muzyczka, Ph.D., University of Florida (*via teleconference*);

Dr. Corrigan-Curay explained that the National Science Advisory Board for Biosecurity (NSABB) had identified biosafety oversight of synthetic biology as an area of concern in their report to the Federal Government on synthetic genomics. The U.S. Government adopted this recommendation and tasked NIH with ensuring that the *NIH Guidelines* explicitly address the biosafety principles and practices applicable to synthetic genomics and biology. Synthetic biology refers to the use of synthetic genomes in biological systems. The RAC Biosafety Working Group had been asked to consider the application of the *NIH Guidelines* to synthetic biology—that is, to determine to what degree this technology is covered and whether the scope needs to be modified to capture synthetic biology—and to develop draft recommendations regarding principles and procedures for risk assessment and management of research involving synthetic biology.

On behalf of the RAC Biosafety Working Group, Dr. Rosenberg presented the proposed changes to the *NIH Guidelines* to cover issues related to synthetic biology. The Working Group has focused on three overarching themes:

- Capture the same products made by synthetic techniques that are currently covered under the scope of recombinant DNA research, provided the same biosafety concerns are raised, with the level of review based on risk and not technique

- Develop a risk management framework based on the current science and what appears to be feasible in the foreseeable future

- Recognize that all future scientific developments cannot be anticipated and that the *NIH Guidelines* may need periodic review

Dr. Rosenberg presented and then explained each of the proposed changes. The scope of the *NIH Guidelines* was modified to clarify the applicability to synthetic nucleic acids. The definition of recombinant DNA molecule was extended to nucleic acids and a definition was added for synthetic nucleic acids that are chemically synthesized or amplified and may solely or partially contain functional equivalents of nucleotides. She described the other proposed changes to the sections on exempt experiments, risk assessment and Major Actions. She noted that significant time was spent discussing whether there is sufficient distinction between the risks of research with replicating vs. nonreplicating synthetic agents to warrant an exemption from the *NIH Guidelines*, and the Biosafety Working Group wrestled with the question of whether there are classes of nonreplicating molecules used in human gene transfer that should be exempt due to lower potential risks and the criteria that should be applied to determine which classes should be exempt.

A. RAC Discussion

In response to the recommendations of the Biosafety Working Group, the RAC discussed the biosafety considerations related to the proposed exemption for non-replicating synthetic nucleic acids including the difference in biosafety risks between replicating and nonreplicating vectors, efficiency of replication in the laboratory and whether replication incompetent integrating vectors and expression cassettes encoding harmful proteins that could be injected by accident posed heightened concerns. The RAC emphasized the need for appropriate practices even for molecules exempt from the *NIH Guidelines*. They noted that the research community and public would be asked to comment on the proposed changes.

B. Committee Motion 5

It was moved by Dr. Kirchhoff and seconded by Dr. Grant that the RAC support the revisions to the *NIH Guidelines* as proposed by the RAC Biosafety Working Group. The vote was 14 in favor, 0 opposed, 0 abstentions, and 0 recusals.

C. Next Steps

After this RAC review of the Biosafety Working Group's draft work products, Dr. Corrigan-Curay described the subsequent steps that begin with a notice in the *Federal Register* that will provide an opportunity for public comment and engagement of stakeholders and other experts. The RAC then will receive the final language for approval of the proposed changes, hopefully in September 2008. After RAC final approval, the recommendations will be conveyed to the NIH Director and the DHHS leadership, with a target date of the end of 2008.

VII. Day 1 Adjournment

Dr. Kodish adjourned Day 1 of the March 11-12, 2008, RAC meeting at 4:30 p.m. on March 11, 2008.

VIII. Day 2 Call to Order and Opening Remarks/Dr. Strome

Dr. Strome, Acting RAC Chair, opened Day 2 of the March 11-12, 2008, RAC meeting at 8:15 a.m. on March 12, 2008.

IX. Gene Transfer Safety Assessment Board Report (GTSAB)

RAC Reviewers: Drs. Albelda, Federoff, and Strome

Dr. Strome reported that, of the 18 protocol submissions received by the OBA in the past 3 months, 14 were not selected for public review and the other 4 were being reviewed at this RAC meeting. Of the 14 protocols not selected, 13 are for cancer, and 1 is for peripheral artery disease; 3 employed a retroviral vector, 3 employed a plasmid, 3 employed a poxvirus vector (canary pox or vaccinia), 2 employed an Ad vector, 2 employed a lentiviral vector, and 1 employed herpes simplex virus vector.

A total of 151 amendments were received by the OBA during this 3-month period, including 56 PI or site changes, 59 annual reports, and 23 others (changes in status and protocol design modifications). Two amendments were discussed briefly:

- **Protocol #0510-740, A Phase I Safety Study in Subjects with Leber Congenital Amaurosis (LCA) Using Adeno-Associated Viral Vector to Deliver the Gene for Human RPE65 into the Retinal Pigment Epithelium.** This protocol was reviewed by the RAC at its December 2005 meeting. One of the recommendations made concerned data sharing and establishment of a common DSMB for Protocol #0510-740 and a similar study being conducted at the same

institution for adults with LCA. The investigators have worked to establish the recommended collaboration, and some of the preclinical data in support of the adult trial has been published; therefore, those data are available to the investigators. The investigators for Protocol #0510-740 also have performed additional preclinical toxicology studies. At this time the trials will proceed with independent DSMBs.

- **Protocol #0710-877, A Phase II Safety and Efficacy Study Evaluating Glutamic Acid Decarboxylase Gene Transfer to the Subthalamic Nuclei in Subjects with Advanced Parkinson's Disease.** This protocol was reviewed by the RAC at its December 2007 meeting. There are a number of differences between this Phase II study and the earlier Phase I trial (Protocol #0104-469, Subthalamic GAD Gene Transfer in Parkinson's Disease Patients Who Are Candidates for Deep Brain Stimulation). Therefore, the RAC recommended that the investigators consider an initial safety study with a small cohort of participants prior to proceeding to the full Phase II randomized controlled trial. The investigators for Protocol #0710-877 replied that they appreciated the RAC's recommendation and would discuss with the FDA whether such a design is warranted. A number of suggestions were made by the RAC regarding the informed consent, all of which have been incorporated by the investigators.

Dr. Strome discussed the AEs that were reported to the OBA during this reporting period. A total of 160 SAEs were reported from 26 trials, of which the overwhelming majority were unrelated to the gene transfer products; there were 31 initial and followup reports in which the SAE was possibly related to the gene transfer products. The GTSAB reviewed 18 initial and 19 followup AEs from 14 trials.

X. Discussion of Human Gene Transfer Protocol #0801-890: A Phase I, Single-Center, Open-Label, Dose-Escalation Study to Evaluate the Safety and Tolerability of GHRH DNA Plasmid (VGX-3200) + Electroporation in Adults with Cancer Cachexia

Principal Investigator:	Rammurti T. Kamble, M.D., The Methodist Hospital/Baylor College of Medicine
Additional Presenters:	Ruxandra Draghia-Akli, M.D., Ph.D., VGX Pharmaceuticals; Cheryl Jo White, M.D., VGX Pharmaceuticals
Sponsor:	VGX Pharmaceuticals
RAC Reviewers:	Drs. Bartlett, Kahn, and Strome

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

A. Protocol Summary

Complications of cancer such as weakness, weight loss (cachexia), and anemia are present in more than half of affected patients. Other clinical manifestations include loss of appetite, muscle wasting, loss of fatty tissue, and tiredness, all of which result in poor quality of life. Cancer cachexia occurs in about 80 percent of advanced cancers and accounts for 20 percent of deaths. Essentially, patients starve themselves and cannot cope with additional treatment, thereby reducing general function, quality of life, and ability to respond to chemotherapy. The presence of cancer cachexia is defined in this protocol as 5-percent weight loss over a 12-month period.

The purpose of this Phase I study is to evaluate the safety and tolerability of escalating doses of plasmid DNA expressing human growth hormone releasing hormone (hGHRH), VGX-3200, administered by intramuscular injection followed by electroporation to research participants with cachexia due to metastatic cancer. GHRH stimulates the synthesis and secretion of GH from the anterior pituitary that in turn stimulates insulin-like growth factor-I (IGF-I) production; furthermore GHRH has direct actions on tissues, such as immune cells. These molecules have been previously used to treat conditions associated with metastatic cancer, but their adverse effects (associated with protein peaks and troughs) may be detrimental. A gene therapy approach will overcome the primary limitation to GHRH use (short half-life in serum), and a single injection into the subject's skeletal muscle of a plasmid GHRH may ensure

physiologic expression of GHRH for 3-12 months. In a series of studies on dogs with spontaneous malignancies, GHRH was efficiently expressed, and induced increased hemoglobin and hematocrit levels, increased quality of life and survival. In mouse studies with implanted tumors, the plasmid mediated GHRH treatment produced significant physiological changes in IGF-I, decreased tumor growth, prevented cachexia, with no discernable adverse effects.

The secondary objectives of the study are: to estimate the clearance rate and maximum concentration of hGHRH achieved by this treatment; to determine whether the rise of serum hGHRH level is proportional to the amount of plasmid electroporated; to evaluate the effects of VGX-3200 on: weight; lean and fat body mass; hematological parameters; fasting serum chemistry; lipid profiles; and appetite.

B. Written Reviews by RAC Members

Five RAC members voted for in-depth review and public discussion of this protocol. Key issues included concerns about the safety of long-term expression of GHRH and the fact that the gene expression system is not capable of being turned off.

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

Dr. Bartlett asked the investigators to interpret GHRH antagonist studies related to this proposed protocol, provide additional insight into the underlying biology of ectopically expressed GHRH, explain the rationale for broad inclusion criteria rather than more restrictive disease-specific criteria, and provide data if available as to the use of GHRH in conjunction with hormonal therapy. A gender bias in response was seen in animal models; he requested that the investigators provide additional data and insight about that result. Dr. Bartlett also asked for data regarding the efficiency of GHRH secretion from skeletal muscle and how its binding and retention in the extracellular matrix of the muscle might influence data interpretation or participant safety. He requested a detailed standard operating procedure for VGX-3200 administration to answer various questions about choice of target muscle, participant age, and the use of two different injection sites. Dr. Bartlett also asked for preclinical data on the use of bupivacaine to locally destroy muscle fibers expressing GHRH, on the continued efficacy of ongoing chemotherapies in the context of GHRH therapy, and on the frequency of vector integration within the target cells. He suggested that the investigators alter the informed consent document to indicate that the injection site will be permanently marked.

Dr. Kahn asked about the impact of participating in this study on participants' potential participation in chemotherapy or other cancer-related trials, both simultaneously and consecutively. Regarding the informed consent document, he offered specific comments and questions to assist the investigators in clarifying this document, including who is paying for the costs of the study, how many visits will be required, the frequency of blood tests, the use of treatment-related language, how women of childbearing potential can participate in this trial, and the disclosure of personal medical information.

Dr. Strome asked the investigators to clarify why they cited a trial in which a recombinant GHRH analog was successfully employed to treat cachexia in patients with acquired immune deficiency syndrome (AIDS) patients and then concluded that such a treatment would not be feasible in cancer patients. He asked for additional data to allay concerns that this drug might enhance tumor growth and for more detailed information regarding the CELLECTRA™ device, in particular whether human trials show superiority of the drug-device combination compared with the drug alone. Noting the likelihood of no therapeutic benefit from this drug regarding tumor regression, Dr. Strome requested that the investigators discuss the ethics of dosing research participants who might then be excluded from other trials that would offer potential clinical benefit.

C. RAC Discussion

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

- Ms. Shapiro suggested that the investigators not restrict participants' reproductive freedom any longer than necessary; thus, the use of birth control should match the real risk of approximately 6 months of plasmid presence. Dr. Zaia noted further that the institutional review board at his institution believes it is particularly insensitive to require a participant who is dying and who probably cannot become pregnant to acknowledge that they will not try to get pregnant for 1 year, when she may not be alive for another year.

- Dr. Strome recommended that the investigators use the appropriate protein as a control if they wish to state that their molecule does not enhance tumor growth. That statement cannot be made when using a human protein in a mouse.

- Drs. Albelda and Strome commented that the target population is so sick that it will be difficult to sort out the natural history of the disease, and the investigators are likely to encounter many side effects that may or may not be related to the drug. Dr. Albelda suggested establishing a "pseudo-placebo" group of patients so as to have a record of the kind of SAEs to be expected from this patient population.

- Dr. Williams suggested adding to the informed consent document that participation in this trial might preclude participation in other Phase I trials—investigators in other cancer trials might not allow participants from this trial to be enrolled because of confusing data regarding tumor growth.

- Dr. Weber suggested excluding potential participants who, due to their tumors, e.g., head-and-neck cancer, can not eat as this will confound the efficacy results.

- Dr. Strome suggested that the investigators give participants camera phones and ask them to take pictures of their food intake with a ruler to produce an independent measure of what they are eating in addition to a food diary. He has used this technique in a number of nutrition trials and it has worked well.

- Dr. Zaia asked whether cancer cachexia patients can make growth hormone or whether the cachexia affects the ability to make a growth hormone. Dr. Zaia suggested that the investigators include among their eligibility requirements that potential participants not be allowed in the trial unless they can make growth hormone.

D. Investigator Response

1. Written Responses to RAC Reviews

The investigators reviewed the results of preclinical research and clinical findings, concluding that the findings suggest that cachectic patients start with a dysregulated baseline level of GHRH/IGF-1. In preclinical animal models, plasmid-delivered GHRH brings the levels of these hormones into the normal physiological range without an increase in incidence or progression of cancer. In addition to increasing IGF-1 levels, growth hormone also increases the serum levels of IGF binding protein 3, the levels of which have been shown, in several epidemiological studies and one study on colon cancer, to be negatively correlated with the risk of cancer. Since growth hormone-treated patients often have subnormal IGF-1 serum levels, which normalize on therapy, the investigators predict that their cancer risk on growth hormone therapy should not increase above that of the normal population.

Regarding tumor growth in the dog studies (using companion animals with spontaneous malignancies), the investigators noted that administration of the GHRH plasmid was not associated with accelerated tumor growth. On the contrary, the beneficial effects on the hematologic, immunologic, and nutritional status of the dogs may have permitted them to tolerate higher doses of chemotherapeutic agents, with the potential to diminish tumor size. The dog model is believed to be an appropriate animal model for cancer cachexia in humans. Similar responses were seen in mice with implanted tumors.

The investigators noted that patients with AIDS cachexia, in whom the causal mechanisms likely overlap with cancer cachexia, have benefited from stimulation of the growth hormone/IGF-1 axis. GHRH agonists with a longer half-life than what is proposed in this study have been used in AIDS patients.

The investigators explained why they prefer to offer this protocol to individuals with a broad range of advanced cancers and associated cachexia. Inclusion of all solid tumors is common practice for Phase I studies, unless a clear rationale exists for selecting a more limited range of tumors. In this case, the investigators believe that the mechanisms that cause cancer cachexia are likely to be common to many tumors and that all have the potential to benefit from restoration of growth hormone production.

Regarding the potential increased risks to participants on hormonal therapies, the investigators stated that the circumstances in which both cancer-specific therapy and hormonal therapy would be given together are rare, with the exception of prostate cancer in men. They further explained that estrogens and the selective estrogen receptor modulators tamoxifen and raloxifene have been used previously to suppress circulating IGF-1 levels in patients with acromegaly. The estrogens might block the effects of GHRH; therefore, the risk for participants in this trial would be that the plasmid-mediated experimental treatment would be less effective when administered in combination with any of these compounds.

In previous studies that measured glucose and/or insulin levels in cows, pigs, horses, and dogs, the investigators found no significant change in those values associated with the plasmid-mediated GHRH treatment. Nevertheless, participants in this protocol will have their glucose and insulin levels monitored and the dose of insulin or hypoglycemic drug will be adjusted accordingly.

GHRH is well secreted into the bloodstream from the skeletal muscle, which the investigators stated that they have assessed through *in vitro* experiments and *in vivo* in mice. Although the investigators cannot rule out the possibility of GHRH binding to the extracellular matrix, they have not observed this phenomenon in animal models.

The investigators explained that they have worked extensively on the optimization of plasmid delivery by electroporation. All the required parameters have been investigated in large-animal models (e.g., farm pigs at different ages), and the currently proposed protocol is based on their experience as well as on data in the literature. The investigators have replicated this procedure successfully in dogs with cancer cachexia. Two potential injection sites are proposed for this trial, to allow for participant preference and for the fact that some individuals may have a significantly reduced deltoid muscle size that would not allow for injection and proper electroporation. The electroporation device has been tested in a trial with healthy volunteers to assess the feasibility of the technique; deltoid muscles were used in this study, and the procedure was generally well tolerated.

Dr. Kamble and his colleagues stated that they have decided not to tattoo the injection site or use bupivacaine to inactivate the GHRH plasmid, in the rare instance that excess secretion of growth hormone occurs. Instead, participants will be treated with the dopamine agonist bromocriptine, which inhibits secretion of growth hormone from the pituitary and is an approved oral therapy for acromegalic patients.

The investigators noted that the design of their plasmid does not support integration into the transfected cells. Preclinical data showed that plasmid numbers decreased as time progressed postvaccination, indicating lack of integration into the tissue. In addition, no microscopic evidence of muscle cell transformation was noted in any of the test animals.

Regarding the ethics of including participants in this trial in relation to their ability to participate in other trials with potential clinical benefit, the investigators reiterated that potential participants will be excluded from this study if they have participated in any investigational trials fewer than 30 days prior to enrollment. Thus, participants in this trial will have failed all available treatments and will have a life expectancy of less than 6 months. If a new therapeutic study opens after participants have been enrolled, the PI will review safety concerns on a case-by-case basis. This protocol does not require that participants avoid

chemotherapy or radiation therapy indicated by medical need, even after enrollment. The investigators will continue to monitor for safety any former participants who enter other investigational studies.

2. Responses to RAC Discussion Questions

Dr. Kamble explained that, when the investigators first proposed this trial, they asked that potential participants wait 7 days from the last dose of chemotherapy before enrolling in the protocol. However, because this is a first-in-human study, the FDA suggested that it would be less confounding to have the side effects of previous treatment taper off to better monitor the safety profile. Therefore, the investigators believe it is appropriate to start this study about 1 month from a participant's last dose of chemotherapy to better monitor the toxicity profile and the safety issues in these individuals.

Regarding requiring birth control up to 1 year postparticipation, Dr. White explained that the plasmid is not likely to be present for any longer than 6 months, so the investigators conservatively added another length of time after that period. The investigators performed extensive preclinical toxicology studies with IM injection and electroporation of plasmid; evaluation of all body sections, including ovaries and testicles, showed no sign of plasmid at any location other than the injection spot.

Dr. Draghia-Akli explained that many studies have been performed with recombinant GHRH using human or porcine GHRH in mice and rats, showing biological effects. The biological effects are not long lasting because the rodents eventually develop antibodies against the porcine or the human GHRH; this effect is dose dependent. Nevertheless, the investigators have shown in previous preclinical work that neutralizing antibodies to human GHRH begin to appear approximately 21 days after injection.

Regarding the possible link between GHRH administration and leukemia, Dr. Draghia-Akli acknowledged that the literature suggests the possibility of such a link in children who received radiotherapy. A definite link between growth hormone administration and cancer development could not be made, and the data in the literature are controversial on this issue. Most studies are not showing a difference of incidence in cancer in children who are matched for various factors, including age, and who receive or do not receive GHRH.

Dr. Draghia-Akli provided additional detail regarding the studies of IGF-1 levels in GHRH-treated dogs and in tumor-bearing mice. In one study called "effects of plasmid GHRH on dogs with cancer," published in *Molecular Therapy*[2], dogs were administered the GHRH plasmids that encode for GHRH analogs. Results indicated that 75 percent of the dogs had IGF-1 increases of 21 percent to 120 percent compared with baseline. Normal IGF-1 levels in dogs are between 50 and 120 nanograms (ng) per mL and, at baseline, these experimental dogs had on average about 40 ng/mL; throughout the duration of this study, those dogs had increased IGF-1 levels, to approximately 70 ng/mL. The dogs on placebo had a decrease in their IGF-1 levels, and the treated animals had an increase in their IGF-1 levels during the study. These animals again were treated with a GHRH analog. The IGF-1 levels decreased in both the tumor-bearing mice (nude mice implanted with human tumor lines) treated with a plasmid human GHRH as well as the control animals. However, the animals that received the GHRH plasmid had a decrease in their IGF-1 levels that was not as dramatic as that in the control animals.

Dr. White agreed to take under consideration RAC members' suggestions to document participants' growth hormone and IGF-1 levels at enrollment, to provide comparison data.

Dr. Draghia-Akli reiterated that the investigators plan to use a muscle-specific promoter rather than a ubiquitous promoter to overcome some of the shortcomings of ubiquitous promoters relative to the persistence of expression levels.

Regarding whether cancer cachexia patients can make growth hormones, Dr. Draghia-Akli responded that the answer to that question is currently unknown. Protein synthesis and deposition are affected in

[2] Draghia-Akli R et al. Effects of plasmid-mediated growth hormone-releasing hormone in severely debilitated dogs with cancer. *Mol Ther* 2002 6(6):830-6.

cachexia, but with better nutrition and the stimulation to normal levels of IGF-1 that the investigators propose will occur, they are also hoping to see protein synthesis and deposition. In the mouse studies, approximately 50 percent of the control animals developed cachexia during the study, whereas none of the GHRH-treated animals developed cachexia.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

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

Preclinical Issues

- The primary safety concern raised by the protocol is the potential of the vector construct, VGX-3200, to promote tumor growth through the increase in the production of IGF-1. The role of IGF-1 in cancer has been recognized in both experimental and clinical settings. Moreover, GHRH antagonists have been shown to suppress tumor growth, suggesting that GHRH could promote tumor growth. Although preclinical data were presented showing that VGX-3200 inhibited tumor growth, which would allay the concern about the role of VGX 3200 in promoting tumor growth, the data were from a mouse model that used human GHRH. This model, due to sequence differences between human and murine GHRH, may not be an accurate predictor of the vector construct's role in promoting human tumor growth. Therefore, additional preclinical studies should be conducted in a homologous system (i.e., murine GHRH constructs in murine tumor models). Human GHRH can be used in the murine model as long as the human GHRH is functionally equivalent to the murine GHRH. In any case, it is also important to select a tumor that is responsive to IGF-1.

- In addition to using the functional endpoints of the transgene to evaluate VGX-3200 in the preclinical studies (i.e., increases in hormone levels), it would be helpful to take measurements of messenger ribonucleic acid levels in the muscle after vector injection to better elucidate the persistence of transgene expression.

Clinical/Trial Design Issues

- Given that there is likely no therapeutic benefit of the gene transfer with respect to tumor regression, the exclusion criteria should not suggest that subjects may not be able to enroll in another clinical trial should one become available.

- Although the protocol cites studies of a recombinant GHRH analog that were successful in treating cachexia in AIDS patients[3], it does not explain why the approach would not be applicable in the treatment of cancer-induced cachexia. If the tolerability of daily subcutaneous injection of GHRH analogs is a problem in terminal patients with cancer cachexia, this point should be made in the protocol and in the consent form.

- The study's hypothesis is that VGX-3200 will lead to increased circulating levels of GHRH, which in turn will stimulate endogenous production of GH. However, no data were provided showing that patients with cachexia are able to produce growth hormone. As such, prospective subjects should be screened to ensure that they are capable of producing growth hormone. At the same time, it also may be important to exclude patients with baseline levels of IGF-1 that are elevated. Since one of the endpoints in evaluating biological feasibility is a change in levels of IGF-1 from the baseline, the feedback mechanisms in the GHRH/GH/IGF-1 axis may preclude additional increases in IGF-1 even in the face of increase in GHRH. In either case, enrolling subjects with too much or too little of these hormones is scientifically and ethically inadvisable. Since valid data are unlikely to result, such subjects should not be asked to undertake the risks of the protocol.

[3] Falutz J et al. Metabolic effects of a growth hormone-releasing factor I patients with HIV. *N Engl J Med* 2007 (357(23):2359-70.

- Life expectancy of at least 3 months is an inclusion criterion. Given the gravity of their underlying disease, such patients are likely to experience a number of AEs that may complicate the interpretation of safety data. Enrolling subjects with a longer life expectancy or incorporating a control group of similarly ill cancer patients without cachexia may be necessary to produce analyzable data.

- Since one of the objectives of the study is to assess the effect of VGX-3200 on body weight, it may be necessary to exclude subjects who cannot maintain adequate nutrition orally or by gastrostomy tube.

- Using food diaries to measure and document food intake may be inadequate. Incorporating photography may provide more reliable quantitative data.

Ethical/Legal/Social Issues

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

- The risk of possible tumor progression caused by gene transfer should be placed at the beginning of the section on risks since it is such a critical risk in this population.

- Although enrollment in this clinical trial will not preclude a subject from trying to enter another therapeutic clinical trial, the subjects should be informed that their participation may preclude them from enrollment in other experimental treatments given that most cancer trials would exclude subjects who have participated in a trial that has a potential to enhance tumor growth.

- It may be helpful to create a chart or timeline outlining visit number, month since enrollment in which each visit will occur, procedures/exams that will be performed during each visit, etc. In particular, the schedule for imaging during the protocol needs to be clarified.

- The investigators should consider amending the requirement that subjects use birth control from 1 year to 6 months given the plasmid's half-life and the reality of the subjects' clinical situations.

- The terms "treatment" and "study doctor" are used inappropriately and should be replaced so prospective subjects are not misled about the protocol's anticipated benefits.

- The institution's policy for managing role conflicts that may occur if the investigators are also serving as a subject's treating physician should be discussed in more detail.

G. Committee Motion 6

Dr. Strome summarized the comments and concerns of the RAC to be included in a letter to the investigators and the sponsor. It was moved by Dr. Kahn and seconded by Dr. Albelda that the RAC approve these summarized recommendations. The vote was 14 in favor, 0 opposed, 0 abstentions, and 1 recusal.

[At this point in the meeting, Dr. Zaia assumed the duties of Acting RAC Chair.]

XI. Discussion of Human Gene Transfer Protocol #0801-897: A Phase I/II, Multicenter, Open-Label, Dose-Escalation Study to Evaluate the Safety and Tolerability of DVC1-0101 Administered Intramuscularly in Subjects with Stable Peripheral Artery Disease

Principal Investigator: Brian H. Annex, M.D., Duke University

Additional Presenters:	Akihiro Iida, DNAVEC Corporation; Yoshikazu Yonemitsu, M.D., Ph.D., Kyushu University
Sponsor:	DNAVEC Corporation
RAC Reviewers:	Drs. Fan, Weber, and Zaia
Ad hoc Reviewer:	Brian R. Murphy, M.D., NIAID, NIH

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

A. Protocol Summary

In the United States, peripheral artery disease (PAD) affects up to 10 million people; however, because approximately half of all patients with PAD exhibit no manifestations of the disease, the actual prevalence is likely much higher. PAD is usually caused by obstruction of blood flow in arteries and most frequently affects lower limb circulation. The advanced stages of PAD can result in severe pain in the lower extremities at rest, loss of tissue, and amputation. Revascularization surgery is currently considered the best option for most patients with advanced PAD, although the failure rate of this surgery is highly variable. Few nonsurgical options exist to provide significant benefit for those patients who are not good candidates for revascularization surgery.

Stimulating new vessel growth from existing vascular structures to increase the blood flow around obstructed blood vessels in limbs (angiogenesis) provides an attractive way to restore blood flow to oxygen-starved tissues. Restoring blood flow to tissues may alleviate symptoms and prevent disease progression; therefore, angiogenic therapy may provide benefit to a large number of patients with moderate to advanced PAD. Fibroblast growth factor 2 (FGF-2), one of several angiogenic growth factors that stimulate development of new blood vessels, has been shown to improve blood circulation in animal disease models.

DVC1-0101 is a drug product composed of Sendai virus (SeV) delivering the human FGF-2 (hFGF-2) gene into human cells. SeV is a mouse virus that can infect human cells but has not been shown to cause disease in humans. DNAVEC Corporation has further manipulated SeV to create a virus that cannot spread from cell to cell and has conducted several *in vitro* and *in vivo* animal studies to investigate the expression, secretion, and angiogenic activity of hFGF-2 using SeV as a delivery vector. These studies demonstrated that intramuscular (IM) injection of DVC1-0101 resulted in robust hFGF-2 transgene expression and activity levels in cells. Experiments in animals also have shown that DVC1-0101 is effective in treating ischemic-diseased tissues and is safe. DVC1-0101 is currently being investigated in a clinical study at Kyushu University Hospital in Japan.

In this proposed Phase I/II study in the United States, DNAVEC Corporation proposes to test DVC1-0101 in research participants with advanced but stable PAD in a multicenter, open-label, dose-escalation study to evaluate the safety and tolerability of DVC1-0101 administered by IM injection. Safety will be assessed by monitoring the frequency, severity, and duration of AEs and clinically significant changes in laboratory parameters of safety. The secondary objectives include determining the pharmacokinetic profile of DVC1-0101 and assessing preliminary efficacy by measuring changes in limb hemodynamics and quality of life and by monitoring specific cardiovascular events, limb retention, and revascularization.

B. Written Reviews by RAC Members

Twelve RAC members voted for in-depth review and public discussion of this protocol. Key issues included the first use of the novel SeV gene transfer vector in a clinical trial in the United States.

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

Dr. Fan asked about the possibility that coinfection with another enveloped virus could spread the SeV vector by pseudotyping. He wondered whether infection with human parainfluenza virus type 1 (HPIV-1) or other viruses that could pseudotype SeV should be an exclusion criterion, given that IV injection of the SeV vector in animals resulted in the infection of multiple organs, including the lung. Dr. Fan also asked

the investigators to provide information about how immune responses to the SeV vector would be distinguished from immunity to prior HPIV-1 infection.

Dr. Weber offered his concerns regarding this protocol, including the investigators' decision to permit dose escalation if one participant experiences an SAE, the need for elaboration on the choice of the different doses to be tested, the use of only a 2-week followup period for assessing safety prior to dose escalation, the frequency of pregnancy testing during the study and on followup, the types of pain relief to be offered to participants, and justification for an endometrial biopsy. His concerns about the informed consent document included the lack of description of the risks due to the required colonoscopy and mammography, inappropriate wording regarding possible benefit to participants, and clarification of several inconsistencies found throughout the document regarding birth control for both men and women.

Dr. Zaia expressed several concerns about the design of the clinical trial, including a request for justification for the use of a 14-day observation period before proceeding to the next dose, extension of the time between dosings within the same cohort, the mechanics of operating this study as a multicenter trial, inclusion of participants with liver enzymes up to three times the upper limit of normal, and whether the proposed study is powered adequately to answer the question of efficacy. He noted that the investigators' response to Appendix M of the *NIH Guidelines* contains a well-calculated discussion of the minimal level of gene transfer/expression necessary for the gene transfer to be considered successful in humans, and Dr. Zaia requested that the investigators present this information at this RAC meeting as a model for other investigators. Dr. Zaia also asked the investigators for additional explanation of the data that indicated a possible gender effect in response to the vector injection and lower background level of FGF in females.

Dr. Murphy noted that the replication-defective SeV vector should not directly cause illness, nor should a replication-competent derivative virus be generated in the human host; in addition, the parainfluenza viruses have not been associated with integration into the host genome. He asked the investigators to explain the implications of previous infection of the human host with the antigenically related HPIV-1. Specifically, Dr. Murphy expressed two concerns related to previous infection: (1) that efficacy data derived only from an evaluation of the SeV vector in an immunologically naive host would not be directly applicable to an immunologically experienced human host and (2) that prior immunological experience with the virus would predispose a research participant to developing an accelerated and augmented immunological response at the site of virus inoculation. Dr. Murphy also asked the investigators whether they were planning to perform pre-inoculation and post-inoculation neutralizing antibody titers to SeV.

C. RAC Discussion

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

- Dr. Albelda asked the investigators to explain why they expect this vector to perform better in this trial than the many other vectors in many other trials for peripheral vascular disease that have not shown benefit.

- Dr. Murphy reiterated that the efficacy of this particular vaccine has not been tested in a host that immunologically mimics the human host.

- Drs. Murphy, Weber, and Zaia expressed concern about the immediate followup period, which is planned for days 0, 2, and 7. All three reviewers suggested that the possibility of an evolving skin reaction resulting from an immunization should be examined with greater frequency. Dr. Murphy suggested taking detailed inventories of reactions and progress at least for the first 10 days and seeing the participants every other day during that time, to document any problems or skin responses. Dr. Strome suggested some kind of home measurement and teaching the participants what to look for and how to self-monitor any reactions.

D. Investigator Response

1. Written Responses to RAC Reviews

The investigators explained that, unlike *in vitro* experiments, the possibility of pseudotyping of SeV vector by another virus *in vivo* in the clinical setting is remote. In addition, detection of SeV-specific RNA does not ensure "infection" or the presence of live, replicating particles in the tissue, because these signals could have been generated from dead or degraded viral particles or debris. Therefore, the investigators did not include active viral infection as an exclusion criterion in this study, although they offered to exclude potential participants showing symptoms of an active upper respiratory tract infection.

The investigators acknowledged that they do not have qualified technology that can distinguish immune responses to the SeV vector from immunity to prior HPIV-1 infection. Because the immune cross-reactivity between these viruses is extensive, the investigators propose to use the same ELISA test (developed originally for SeV) to measure the antibody level in preinjection and postinjection sera; they plan to regard the elevation of antibody level after DVC1-0101 administration as the immune response specific to the SeV vector.

Regarding prior exposure to HPIV-1, the investigators explained that it has been well documented that the majority of the general population has been exposed to HPIV in childhood and therefore should have antibody titers against HPIV. They acknowledged that it is reasonable to conclude that preexisting immunity to HPIV-1 may have an impact on the challenge of SeV vector in this clinical study. Although no direct evidence exists to show what effect preexisting antibody levels may have on the expression of FGF-2 from DVC1-0101, some indirect data suggest that SeV vectors can infect and express a transgene in patients with preexisting antibodies to HPIV-1.

In a study conducted by the investigators in which mice were primed intramuscularly with SeV vector and then were challenged intranasally with a second dose of SeV vector, no severe immunological reactions were observed. While the investigators do not consider it likely that DVC1-0101 would elicit a systemic or local accelerated response in participants with preexisting HPIV-1 immunity, as a precaution, the investigators plan to monitor carefully the injection sites of each participant in this trial.

In response to concerns expressed in Dr. Weber's written review, the investigators agreed to revise the protocol so that dose escalation will be prohibited if one participant in a cohort develops a study-related SAE, using the National Cancer Institute Common Toxicity Criteria to grade severity of AEs. In addition, they agreed to extend the observation period between enrolling participants to 14 days and to extend the observation period to 30 days before proceeding to the next cohort. A follow-up period of 30 days is believed to be sufficient to assess safety of the vector because SeV vector is eliminated from infected animals in a relatively short period of time—after day 8 in the rat.

The investigators agreed to perform additional pregnancy tests on women of childbearing potential at the 1-month and 3-month follow-up visits, in addition to pregnancy tests already proposed at baseline and at 6-month follow-up. The possibility that the SeV vector causes any heritable genetic damage is remote, even in the unlikely event that the vector is transmitted to germline cells, because the infection by the vector does not affect chromosomes. The vector is eliminated from the system nearly completely in 2 weeks, minimizing the risk of causing genetic damage to an offspring even if a participant does become pregnant. In addition, a single barrier method of birth control is recommended (as opposed to two such methods).

The DSMB will include at least one vascular specialist, a cardiologist, and an infectious disease physician; because the study is not powered to support clinical significance, a biostatistician is not required at this stage of development.

Regarding the potential for hFGF-2 to cause proteinuria, the investigators acknowledged that proteinuria has been reported in two Phase II trials of IV or intra-arterial administration of recombinant FGF-2; it was speculated that the proteinuria was related primarily to the systemic route of administration and the

frequent dosing schedule. The current proposed trial is an IM, single-dose study, not a systemic therapy. In animals, FGF-2 has not been detected in the blood after an IM injection of DVC1-0101; therefore, the risk of proteinuria should be lower than that observed in studies employing an IV or intra-arterial route of injection and multiple dosing.

Although the primary objective of the proposed study is safety, the investigators stated their belief that it is necessary and ethical to measure clinical efficacy outcomes because the participants have PAD (they are not healthy volunteers). Therefore, the investigators are proposing that this study assess several clinically relevant outcome measures as potential or preliminary signals of efficacy, including changes in limb hemodynamics and the effect on quality of life and limb pain.

2. Responses to RAC Discussion Questions

In response to Dr. Weber's concern, Dr. Annex agreed that the investigators would exclude from participation in this study any individuals who could not give primary consent.

Regarding concerns expressed about the infrequency of the immediate followup period, Dr. Annex noted that more frequent visits to the clinic would not be practical in North Carolina because many of the participants in this trial will likely be traveling for several hours to get to the clinic. Requiring more frequent clinic visits would exclude a large number of potential participants because of that driving distance, especially for something that could be reported by telephone.

Responding to Dr. Albelda's query about why the investigators expect this trial to work when others like it have failed, Dr. Annex explained that there is little doubt conceptually that FGF has the potential to be effective, although whether it will work in humans is debatable. Delivering FGF-2 for 2 days could result in a long-term response if it invokes downstream pathways and initiates some cascades—possibilities that have been understudied. This trial provides a more potent line of investigation and will be testing FGF-2 in an adenoviral vector, which has never been done before.

E. Public Comment

Public attendees offered no comments.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

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

Preclinical Issues

- Since most subjects are likely to have preexisting immunity to HPIV-1, a virus antigenically related to SeV, there should be an assessment of the impact of the immunity on the safety and efficacy of the SeV construct. Preclinical studies of the SeV vector, DVC1-0101, should be conducted in animals with preexisting immunity to HPIV-1.

- Although the vector is replication incompetent, coinfection with other enveloped viruses is possible and, if it occurred, could lead to the spread of the vector by pseudotyping. Preclinical experiments should be performed to determine whether this is indeed possible.

Clinical/Trial Design Issues

- Immune responses to SeV are to be monitored using an ELISA assay for antibodies. However, since an ELISA assay may not be able to distinguish between antibodies to SeV and HPIV-1, it may be prudent to use neutralizing antibody titers to SeV both before and after administration of the vector.

- Immunity to HPIV-1 could cause the SeV vector to trigger a memory T-cell response against SeV infected cells. This would induce an immunological response at the injection sites. The protocol should gather more data on the safety of the construct by conducting studies of the cellular immunity against SeV.

- Since early recognition and treatment of an injection site reaction are so critical, protocol procedures should include a mechanism (e.g., a questionnaire) that would allow subjects experiencing reactions between followup visits to accurately convey that information to the investigators between followup visits. This is especially important in the first 10 days following administration of the vector.

- In elderly patients, certain types of vaccines have caused unusual SAEs, including myocardial infarction. Although these events are rare, the protocol should address this risk, and it should be included in the informed consent document.

Ethical/Legal/Social Issues

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

- Given the level of risk and lack of potential benefit of the protocol, patients who are unable to understand the study and give their informed consent should not be enrolled.

- The consent document should be modified as follows:

    - The risks associated with the digital subtraction angiography procedure should be described in more detail (e.g., the magnitude and probability of the risk should be explained). Separating more common and less serious risks such as pain and bruising from the catheter site from the rare and very serious risks of heart attack, stroke, gangrene, and amputation would be more informative to the subject.

    - The risks to elderly patients of rare side effects associated with certain types of vaccines should be discussed.

    - The consent document should spell out which "routine lab tests" will be performed since some subjects may not regard all such tests as routine. Also, since there will be multiple urine samples collected for pregnancy and other clinical tests, the document should be clear on this point.

G. Committee Motion 7

Dr. Zaia orally summarized the comments and concerns of the RAC to be included in a letter to the investigators and the sponsor. It was moved by Dr. Albelda and seconded by Dr. Fan that the RAC approve these summarized recommendations. The vote was 13 in favor, 0 opposed, 0 abstentions, and 1 recusal.

XII. Appendix M-VI-A of the *NIH Guidelines* (the "Vaccine Exemption"): Discussion of Immunotherapy for Human Papillomavirus

Dr. Strome recused himself from consideration of this discussion due to conflicts of interest.

Presenter: Dr. Corrigan-Curay

Dr. Corrigan-Curay discussed the application of the vaccine exemption section within the *NIH Guidelines* to HPV immunotherapy. Section M-VI-A of the *NIH Guidelines* states: "Human studies in which induction or enhancement of an immune response to a vector encoded microbial immunogen is a major goal, such

an immune response has been demonstrated in model systems and the persistence of the vector encoded immunogen is not expected, are exempt from Appendix M-I, *Requirements for Protocol Submission, Review and Reporting- Human Gene Transfer Experiments*." Studies that meet the three criteria are not required to be submitted to the RAC for review, and none of the resulting safety data are required to be submitted to the OBA. Dr. Corrigan-Curay then provided a short history of vaccine exemption, which is designed to foster the rapid development of vaccines against infectious agents with significant public health impact. Examples of studies that fall under the vaccine exemption, as determined by the OBA, include infectious disease prevention protocols and some HIV therapeutic protocols.

The HPV immunotherapy uses a vector encoding the HPV transforming proteins, E6 and E7, in patients with cervical dysplasia to generate an immune response that will treat dysplastic, precancerous lesions and serves as a potential alternative to surgical excision as a way of preventing cervical cancer. The RAC Vaccine Working Group concluded that the primary goal of HPV immunotherapy is to generate an immune response to an antigen. However, because the transgene is derived from a known viral oncogene and the major goal is to treat precancerous lesions, these protocols are analogous to cancer vaccines and do not fall within the intent of the vaccine exemption under Section M-VI-A of the *NIH Guidelines*.

The members of the RAC Vaccine Working Group were Drs. Dewhurst, Ertl, Federoff, Kirchhoff, Vile, and Zaia.

A. RAC Discussion

The RAC discussed issues concerning vaccine exemption for HPV immunotherapy, including the criteria for exemption, whether the purpose is to kill cancer cells or a virus, the differences between a standard preventive vaccine and a treatment vaccine, and a suggestion to provide some guidance related to the interpretation of the vaccine exemption criteria.

Dr. Weber supported the proposal from the RAC Vaccine Working Group that HPV immunotherapy trials should not fall under the vaccine exemption. He noted major differences between standard preventive vaccines and a treatment vaccine like the one for HPV immunotherapy. Among the differences he noted were many more injections, and intralesional injections that may have complications.

Dr. Albelda summarized his view that if the major goal of vector administration is to prevent an infection, then the related clinical trial falls under the exemption. However, in the HPV case, the vaccine is not intended to target HPV virus but tumor cells expressing the viral antigens.

Dr. Zaia noted the distinction as between measuring the outcome as a reduction in infection or tumor.

Dr. Flint suggested providing guidance related to interpreting the vaccine exemption criteria, which would be helpful to investigators as well as to IBCs.

B. Public Comment

Bentley Moyer, Anza Therapeutics, Inc., noted that HPV lesions are precancerous lesions but that they are not necessarily destined to be cancerous. He asked for a definition of "analogous to a cancer immunotherapy."

A letter dated February 29, 2008, from MGI PHARMA, INC., was entered into the record. Signed by Jenny Zhang, M.D., Ph.D., Medical Director, and Jeffrey L. Peart, Director of Regulatory Affairs, this letter attached a white paper that focused on information about the appropriateness of continuing the vaccine exemption for Amolimogene, an immunotherapeutic agent designed to target HPV-infected cells.

C. Committee Motion 8

Dr. Corrigan-Curay orally summarized the motion: With respect to these protocols for HPV immunotherapy using a vector expressing oncogenes in research participants with potentially precancerous lesions, this research does not fall within the vaccine exemption section of the *NIH Guidelines*. It was moved by Dr. Weber and seconded by Dr. Kirchhoff that the RAC approve the motion. The vote was 11 in favor, 0 opposed, 0 abstentions, and 0 recusals.

XIII. Closing Remarks and Adjournment/Dr. Zaia

Dr. Zaia thanked the RAC members and OBA staff and adjourned the meeting at 1:15 p.m. on March 12, 2008.

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

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

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

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

Date: _____

_____
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Recombinant DNA Advisory Committee

Attachment I
Recombinant DNA Advisory Committee Roster

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Attachment III
Abbreviations and Acronyms

Ad	adenoviral, adenovirus
Ad5	adenovirus serotype 5
ADA-SCID	adenosine deaminase-deficient SCID
AE	adverse event
ALL	acute lymphoblastic leukemia
CHF	congestive heart failure
DHHS	U.S. Department of Health and Human Services
DNA	deoxyribonucleic acid
DSMB	data and safety monitoring board
FA	Fanconi anemia
FANCA	Fanconi anemia complementation group A
FDA	Food and Drug Administration, DHHS
FGF-2	fibroblast growth factor 2
GHRH	growth hormone-releasing hormone
GTSAB	Gene Transfer Safety Assessment Board
hFGF-2	human fibroblast growth factor 2
HIV	human immunodeficiency virus
HPIV-1	human parainfluenza virus type 1
HPV	human papillomavirus
IBC	institutional biosafety committee
ICD	implantable cardioverter defibrillator
IGF-1	insulin-like growth factor 1
IM	intramuscular
IV	intravenous
LCA	Leber Congenital Amaurosis
MAGIC trial	Myoblast Autologous Grafting in Ischemic Cardiomyopathy trial
`NHLBI	National Heart, Lung, and Blood Institute, NIH
NIAID	National Institute of Allergy and Infectious Diseases, NIH
NIH	National Institutes of Health
NIH Guidelines	*NIH Guidelines for Research Involving Recombinant DNA Molecules*
NSABB	National Science Advisory Board for Biosecurity
OBA	Office of Biotechnology Activities, NIH
OD	Office of the Director, NIH
PAD	peripheral artery disease
RAC	Recombinant DNA Advisory Committee
SAE	serious adverse event
SDF-1	stromal cell-derived factor 1
SeV	Sendai virus
SIN	self-inactivating
SKMB	skeletal myoblast
UK	United Kingdom
X-SCID	X-linked severe combined immunodeficiency