RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

March 14, 2007

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]

March 14, 2007

The Recombinant DNA Advisory Committee (RAC) was convened for its 107th meeting at 8:00 a.m. on March 14, 2007, at the National Institutes of Health (NIH), Building 31-C, Conference Room 6, Bethesda, Maryland. Dr. Howard Federoff (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 8:00 a.m. until 5:20 p.m. on March 14. The following individuals were present for all or part of the meeting.

Committee Members

Steven M. Albelda, University of Pennsylvania Medical Center
Stephen Dewhurst, University of Rochester Medical Center
Hildegund C.J. Ertl, The Wistar Institute
Howard J. Federoff, University of Rochester
Jane Flint, Princeton University
Helen Heslop, Baylor College of Medicine
Louis V. Kirchhoff, University of Iowa
Eric D. Kodish, The Cleveland Clinic Foundation
Nicholas Muzyczka, University of Florida
Naomi Rosenberg, Tufts University
Robyn S. Shapiro, Medical College of Wisconsin
Nikunj V. Somia, University of Minnesota, Twin Cities
Richard G. Vile, Mayo Clinic College of Medicine
David J. Weber, The University of North Carolina at Chapel Hill
Lee-Jen Wei, Harvard University

Office of Biotechnology Activities (OBA) Acting RAC Executive Secretary

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

***Ad Hoc* Reviewers and Speakers**

Fabio Candotti, National Human Genome Research Institute (NHGRI), NIH
Jacqueline Corrigan-Curay, OD, NIH
Theodore C. Friedmann, University of California, San Diego
Jay Lozier, Warrant Grant Magnuson Clinical Center, NIH
Harry L. Malech, National Institute of Allergy and Infectious Diseases (NIAID), NIH
Marina O'Reilly, OD, NIH
Elena Pope, The Hospital for Sick Children and University of Toronto *(via teleconference)*
Sanjay Rajagopalan, The Ohio State University *(via teleconference)*
Steven A. Rosenberg, National Cancer Institute (NCI), NIH
Carolyn A. Wilson, Food and Drug Administration (FDA), U.S. Department of Health and Human Services (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.

Nonvoting Agency Representatives

Kevin A. Prohaska, Office for Human Research Protections (OHRP), DHHS
Daniel M. Takefman, FDA, DHHS

NIH Staff Members

Kelly Fennington, OD, NIH
Linda Gargiulo, OD, NIH
Bob Jambou, OD, NIH
Laurie Lewallen, OD, NIH
Maureen Montgomery, OD, NIH
Gene Rosenthal, OD, NIH
Allan Shipp, OD, NIH

Others

There were 57 attendees at this one-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 these Minutes.

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

Dr. Federoff, RAC Chair, called the meeting to order at 8:00 a.m. on March 14, 2007. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (*NIH Guidelines*) was published in the *Federal Register* on February 26, 2007 (72 FR 8387). Issues discussed by the RAC at this meeting included public review and discussion of two protocols, a Gene Transfer Safety Assessment Board report, and presentations and discussions on gene therapy opportunities and challenges for the next decade, thrombosis and malignancy implications for therapy, human cancer immunotherapy using genetically modified autologous lymphocytes, and new developments in X-SCID gene transfer.

Dr. Corrigan-Curay reminded all RAC members of the rules of conduct that apply to them as special Federal Government employees.

II. Minutes of the December 5-6, 2006, RAC Meeting/Drs. Kirchhoff and Vile

After noting a few minor changes, Dr. Kirchhoff stated that the December 5-6, 2006, RAC minutes were a fair representation of the meeting; Dr. Vile concurred.

A. Committee Motion 1

It was moved by Dr. Kirchhoff and seconded by Dr. Vile that the RAC approve the December 5-6, 2006, RAC meeting minutes. The vote was 14 in favor, 0 opposed, 0 abstentions, and 0 recusals.

III. Discussion of Human Gene Transfer Protocol #0612-821: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Ad5FGF-4 in Female Patients with Stable Angina Pectoris Who Are Not Candidates for Revascularization

Principal Investigator:	Matthew Watkins, M.D., Vermont College of Medicine
Additional Presenters:	Randall Moreadith, M.D., Ph.D., Robert L. Engler, M.D., Anthony S. Andrasfay, Patricia L. Novak, Ph.D., Jennifer A. Spinella, MT (ASCP), and Ted Williams; Cardium Therapeutics, Inc.
Sponsor:	Cardium Therapeutics, Inc.
RAC Reviewers:	Dr. Nemerow, Ms. Shapiro, and Dr. Wei
Ad hoc Reviewer:	Sanjay Rajagopalan, M.D., The Ohio State University *(via teleconference)*

A. Protocol Summary

More than 13 million people in the United States have symptomatic coronary heart disease, and since 1984 more women than men have died of cardiovascular disease. More than 6 million U.S. citizens suffer from angina pectoris, with about 400,000 new cases diagnosed each year. New therapeutic options are needed to meet the demands of these patients, who have recurrent chronic angina even following surgery and/or other cardiac interventions for revascularization. An anti-ischemic therapy for control of anginal symptoms is becoming a particularly pressing need for women.

Ad5FGF-4 is an adenoviral vector expressing the human fibroblast growth factor-4 driven by the cytomegalovirus (CMV) promoter. Delivery of FGF-4 to the heart may allow for a more sustained production of the angiogenic protein stimulus potentially to stimulate the growth of new blood vessels and thereby relieve ischemia through improved blood flow. This study is designed to develop a new approach to treat current stable angina pectoris in female research participants who are not candidates for traditional mechanical revascularization and who are on optimal drug therapy.

Ad5FGF-4 has been evaluated in four prospective, randomized, placebo-controlled multicenter clinical trials (Angiogenic GENe Therapy [AGENT]-1 through AGENT-4). The safety database includes 663 research participants (213 on placebo and 450 on Ad5FGF-4) who have been followed for more than 1,700 patient-years. No cases of clinical myocarditis, no evidence of an increase in heart failure, no reports of pathological angiomas, and no retinal neoangiogenesis have been reported. Long-term followup safety data collection to assess the risk of delayed adverse events (AEs) following intracoronary delivery of Ad5FGF-4 is ongoing for AGENT-3 and AGENT-4. In the current followup database from the four AGENT studies, no statistically significant differences have been seen in the incidence of AEs during long-term follow-up.

The protocol is a randomized, double-blind, placebo controlled, parallel group Phase III study that will enroll approximately 300 female patients with stable angina who are not candidates for revascularization. The primary objective of the study is to evaluate the effect of Ad5FGF-4 on myocardial ischemia during exercise treadmill testing (ETT). The safety of Ad5FGF-4 will be assessed by adverse events, clinical laboratory evaluations and long-term follow-up to identify important events occurring 12-60 months after product administration.

B. Written Reviews by RAC Members

Eleven RAC members voted in-depth review and public discussion. Key issues included the safety and efficacy data and the study plan; the effect of preexisting neutralizing antibodies to the adenoviral vector on safety and efficacy; the need for a clear description of the assay used to monitor Ad5FGF-4 preparations for replication-competent adenoviruses (RCAs); the rationale of enrolling only women; the safety profile of the catheter delivery device; the need for sham cardiac catheterization in the control

group; the need for stringent criteria to exclude participants with a history of cancer; and an analysis of long-term followup data on participants of other relevant gene transfer trials.

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

Dr. Nemerow asked for an explanation of the scientific rationale for using FGF-4 rather than any of the other 20 members of the FGF family. He asked the investigators to explain the new assay methodology that resulted in the use of lower vector doses in this proposed Phase III trial compared with previous trials that used higher doses. Dr. Nemerow also requested additional details about the participants who had experienced transient fever following vector administration in previous trials as well as clarification of the pathway of adenoviral infection. He asked whether the investigators had noticed retinal changes in participants in the earlier Phase I and II trials during the long-term followup safety evaluations. Regarding results from the porcine model, Dr. Nemerow asked for more information about the percentage of coronary microvascular endothelial cells transduced by Ad5 vectors as well as the duration of transgene expression.

Because of concerns about the risk-benefit ratio, Ms. Shapiro asked the investigators to address apparent gender differences in earlier Ad5FGF-4 studies, the large placebo effects in angiogenesis trials and to provide updated safety data, including data on the delivery device. Regarding the informed consent document, she asked that the investigators be more precise in their discussion of the most frequent AEs associated with the investigational product to better inform prospective participants about the likelihood of these events. Ms. Shapiro requested additional information about the risks related to, and the need for, administration of a full sham cardiac catheterization to the placebo group. She asked the investigators whether prospective participants at increased risk of harm from the sham catheterization could be identified and excluded, what followup care would be provided to control group participants who suffer harm from the sham catheterization, and to consider fully disclosing, as part of the informed consent process, the rationale for using a placebo arm in this proposed protocol.

Regarding design issues, Dr. Wei requested that the investigators please provide the expected confidence interval(s) for the difference(s) (or the ratio) of two mean event times (the onset time of myocardial ischemia during ETT). He noted that the response variable is the time to event, whose distribution is skewed to the right, so a scale change (or location difference in a log-scale) between two groups would be an interesting summary for the contrast of two comparators. Estimating the size of the difference is more informative than using p-value. He suspected that the study is under-powered with respect to the interval estimation, that is, the low bound of 95% interval for the difference may not be clinically meaningful improvement. He suggested using dynamic treatment allocation rather than having randomization blocked by the centers in order to decrease the possibility of a global imbalance due to the involvement of a large number of centers. Dr. Wei offered four technical statistical suggestions to improve the analysis of the results of this proposed trial. Regarding monitoring issues, to increase the power of the study, he suggested specifying the rules for selecting a particular dose group at the interim monitoring point and assigning 125 (instead of the proposed 100) participants to each dose group, in case one of the three dose groups is terminated at the interim monitoring point. In the case of multiple serious adverse events (SAEs) with one participant, Dr. Wei requested that all the information for the safety data analysis be used, not merely the worst case per participant.

Ad hoc reviewer Dr. Rajagopalan asked about the rationale for use of the lower dose given that there did not appear to be data to support the notion that the higher dose is inferior to the lower dose in all of the AGENT trials. He was concerned about the use of a surrogate secondary endpoint to assess preliminary efficacy. He noted that the rationale for an interim look at 8 weeks is unconvincing, in part because the data from AGENT-2 were not significant at that time point. He suggested that the investigators should clearly articulate the potential safeguards for unblinding, and provide data on baseline covariates that will be controlled for, including adjustments for underlying conditions that may affect the result.

C. RAC Discussion

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

- Dr. Albelda asked about the statistics on tumors in participants who received growth factors, noting that the incidence of cancer vs. placebo for either dose cohort was not statistically significant but did show a trend and would bear watching carefully.

- Dr. Vile asked for further explication of the cancer data for men and women from the AGENT trials.

- Dr. Ertl suggested that the investigators study both male and female animals that are age matched to potential human trial participants.

- Dr. Federoff asked about the rationale for excluding women with a first-degree relative with breast cancer but not excluding women with a first-degree relative with colon cancer if the woman has had a colonoscopy within the past 3 years.

- Dr. Federoff also asked the investigators to discuss what steps they intended to take regarding the possibility of contrast agent-induced nephropathy.

D. Investigator Response

Regarding the female research participant population, the decision was based on analysis of the combined data for females (a pre-specified subgroup) which revealed statistically significant and clinically meaningful changes from baseline for multiple clinical endpoints, including time to electrocardiogram (ECG) ischemia during ETT, total ETT time, time to angina, and Canadian Cardiac Society (CCS) angina classification. While product may also be active in males as demonstrated by the results from the AGENT-2 trial in which the majority of patients randomized were males, in the AGENT-3 and AGENT-4 studies a measurable treatment effect could not be shown in the male subgroup most likely due to the substantial placebo response observed for males but not females. Coronary artery disease (CAD) in females may have different presentations, physician treatment paradigms and subsequent outcomes compared to males. Although the causes of gender differences are not fully understood, differences between males and females with CAD have been observed in the affected coronary vasculature. Thus the hypothesis of more microvascular disease in women could explain both the lower placebo effect and an angiogenic effect of Ad5FGF-4 on the clinical manifestations of microvascular disease.

FGF-4 was selected as the transgene based on preclinical data indicating restored myocardial function and flow to ischemic regions of the heart in the pig ameroid ischemia model and the safety and efficacy data from the four previous clinical trials.

The doses to be administered are actually identical to those used in the previous trials. The apparently lower dose is the result of the use of a more accurate method to measure total viral particle (vp) concentration. The method used previously over-estimated the vp concentration.

The febrile events observed after vector administration were not associated with decreased platelet counts. While cytokine concentrations were measured in the UK and Ireland trials, no febrile events occurred in those trials.

Dr. Moreadith explained that participants in the AGENT trials underwent baseline evaluation by an ophthalmologist and that no retinal changes were seen in participants who received the same experimental product as that proposed for use in this proposed trial.

Regarding the risk of the proposed procedure and its comparison with similar trials, Dr. Watkins explained that more than 660 treated patients underwent the invasive procedure to administer the study product.

Only one individual experienced an SAE (myocardial infarction followed by stroke), and one experienced a transient AE. He stated that this safety profile is comparable with other invasive gene transfer trials.

In response to concerns about the use of a placebo arm in this proposed protocol, Dr. Moreadith explained that contemporaneous angiogenic gene transfer trials that were conducted using proteins or injections confirmed a high placebo response. Therefore, to be able to assess whether this study product is an efficacious treatment, the investigators believe that participants must undergo a placebo-controlled, randomized trial. To make this clear, the investigators have added to the informed consent document a statement that indicates to potential enrollees that there is a one-in-three chance that they will receive placebo and that participants, their physicians, and study personnel will not know which product they will receive. All participants (placebo and both active dose groups) will undergo diagnostic cardiac catheterization in order collect information regarding the presence and extent of coronary disease.

Dr. Watkins stated that, at the point of administration of the study product in the cardiac catheterization laboratory, both the diagnostic procedure and the potentially therapeutic procedure work together; the risks from each are inseparable.

Regarding the effect of pre-existing immunity, in the previous four clinical trials of Ad5FGF-4, participants with pre-existing neutralizing antibodies to Ad5 were not excluded. In each of the studies no consistent relationship between efficacy and baseline neutralizing antibody titers was observed. The only adverse event related to the adeno vector component of the product was transient fever occurring in approximately 8% of participants during the first 1-2 days after Ad5FGF-4 administration.

Responding to concerns about this trial's proposed low and high doses undergoing simultaneous investigation, Dr. Engler clarified that the investigators have preliminary evidence from the AGENT trials that there is efficacy at both the low and high doses and that there may be a dose-response curve. If both doses are effective in the setting of this protocol, then the FDA would mandate use of the low dose because it is lower *and* effective. However, if the investigators study only the high dose and SAEs occur in the high-dose group, then that dose would be found to be unsafe, and no data would have been developed regarding the lower dose.

Dr. Engler reported on the scant available data regarding transgene persistence by describing the results of two autopsies from the AGENT-1 trial. Two participants died subsequent to gene transfer. The autopsies revealed no evidence of excessive angiogenesis, and when polymerase chain reaction (PCR) was conducted on tissue samples from one of these two participants, the transgene was completely gone at 8 to 12 weeks after gene transfer.

Dr. Moreadith conceded that this patient population has increased cancer risk compared with the general population. The cancer types that were seen in the AGENT-3 and AGENT-4 trials included skin cancers (squamous cell, melanoma, and basal cell), breast cancer, colon cancer, prostate cancer, and a few cases of glioblastoma. Dr. Engler assured the RAC that the followup data from the AGENT-3 and AGENT-4 trials as well as data from this proposed trial would be reported completely and promptly to the data and safety monitoring board for this protocol.

Dr. Engler explained why women with a first-degree relative with breast cancer would be excluded but women with a relative with colon cancer would not be excluded. Colon cancer is a slow, progressive disease, the detection levels using colonoscopy are high, and the cure levels with surgery are good when colon cancer is detected early. The American Cancer Society recommends that individuals with hereditary nonpolyposis colon cancer get a colonoscopy every 3 years. On the other hand, even many women who have annual mammograms still develop breast cancer that is metastatic and fatal. This significant difference between breast and colon cancers, along with the high risk in families with breast cancer, explains the investigators' exclusion decision.

With regard to the possibility of contrast agent-induced nephropathy, Dr. Moreadith noted that the contrast load received by study participants will be significantly less than what would occur in a routine

diagnostic procedure. Dr. Watkins added that the use of prophylactic measures to help prevent contrast-induced nephropathy will be part of the investigator training for this protocol.

In response to Dr. Wei's questions, the investigators noted that the distribution of the primary efficacy endpoint (change in time to onset of myocardial ischemia during ETT) is skewed to the right. The estimated mean difference of 40 seconds referred to in the protocol is based on the results of the previous trials, but was not used as the parameter of interest in estimating the required sample size. The parameter of actual interest is the probability that a randomly selected observation from one group will be larger than a randomly selected observation from the other group; this parameter was estimated using the data from the previous trials.

Regarding dynamic randomization, the investigators agreed that could be used to ensure that there will be balance among the three treatment groups with respect to both the total number of randomized patients and the number of randomized patients per center. Dynamic randomization would also be useful (perhaps even essential) if there were a number of known and important baseline prognostic factors for which balance was desired. However, because (a) center is the only stratification variable in this trial, (b) the potential importance of balancing by center is uncertain as we do not anticipate that differences among centers will affect the assessment of study endpoints, and (c) there are major logistical difficulties associated with implementing dynamic randomization, we believe that stratifying the randomization by center, using block sizes of 3 will ensure an adequate balance.

To clarify the safety data analysis, the investigators explained that selected tabulations of AEs will be presented on a per-patient basis (i.e., in terms of proportions of patients who have the specified type of event). In these tabulations, the "worst case" for the specific type of event will be used. However, complete data concerning all SAEs and their timing will be tabulated and summarized in the Clinical Study Report.

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

- A major unresolved issue relates to the dearth of data about the persistence of the transgene and gene expression after intracoronary administration of the vector product, i.e., an adenovirus containing the gene for fibroblast growth factor-4 (Ad5FGF-4). While they would be quite challenging to mount, studies to generate these data would lead to a better understanding of this investigational agent.

Clinical/Trial Design Issues

- The decision to limit enrollment to women in this Phase III study is based on a meta-analysis of the data on the female subgroups from the previous trials with Ad5FGF-4. The meta-analysis found that women had statistically significant and clinically meaningful changes from baseline for multiple clinical endpoints, including time to exercise-induced ischemic changes on ECG during exercise treadmill test, total ETT time, time to angina, and improvement in Canadian Cardiac Society (CCS) angina classification. In contrast to this finding, the sponsor found that the data on the male subjects did not show a measurable treatment effect, which the sponsor attributed, in part, to the substantial placebo response observed for males but not females. While the reasons for the differences were inferred from the meta-analysis, a mechanistic explanation has not been provided. Obtaining a better understanding of the pathophysiologic mechanism(s) behind these

differences should be a priority both for the sponsor and others interested in this particular clinical observation.

- Because a number of subjects in the earlier trials experienced a transient fever following vector administration, cytokine levels should be measured in any subjects who develop a fever after vector administration. Cytokines (IL-6, IL-10 and TNF-α) were measured in one of the previous Phase II studies at sites in the United Kingdom and Ireland. However, the subjects whose levels were measured did not have a fever following vector administration.

- The sample size is estimated based on a nonparametric test with an alternative hypothesis that there may be a 40 second difference between the control and the treatment groups in time to ECG changes indicative of myocardial ischemia on ETT. In order to determine whether the sample size is sufficient to properly power the study (i.e., reach a statistically significant conclusion), an additional calculation needs to be performed. The expected confidence interval(s) for the difference(s) (or the ratio) of two mean event times (the onset time of ECG changes indicative of myocardial ischemia during ETT) should be estimated. Determining the lower bound of the 95% interval for the difference to onset time for myocardial ischemia during ETT is especially important. If the difference does not reflect a clinically meaningful improvement, the study may be underpowered.

- The study design includes an interim analysis using adenosine single photon emission computed tomography with technetium-99m sestamibi perfusion scan for the first 150 subjects (approximately 50 subjects in each cohort) who complete the six month visit. Data from the interim analysis may determine which AD5FGF-4 dose group to carry forward to trial completion. Given that the interim analysis will not result in the stopping of the trial, the decision to use the SPECT perfusion scan, a secondary endpoint, rather than time to ECG changes on ETT, the primary endpoint, should be explained more fully.

- The decision to conduct a SPECT perfusion study at six months, rather than eight weeks as in earlier trials, was made largely on the basis of an expert's recommendation (Daniel Berman, M.D.). While this decision is reasonable, it is important to recognize that there is a paucity of data to support it.

- The meta-analysis of the female subgroups from the earlier studies did not reveal a difference in response to the study agent in subjects taking hormone replacement therapy (HRT). The protocol is expected to be powered enough to detect any potential differences in response related to HRT use and those effects should be monitored and analyzed.

- Given data from the earlier trials showing a trend toward the development of malignancy in subjects who received the Ad5FGF-4 as compared to placebo, the proposed screening and monitoring for neoplasia are important safety precautions. Continued vigilance and analysis of the data with respect to malignancy are critical.

Ethical/Legal/ Social Issues

- The informed consent document should include a specific statement about the possible increased risk of malignancy from the study agent.

- The placebo arm involves a diagnostic cardiac catheterization, a procedure that is not part of subjects' standard medical care. The rationale for the placebo group, i.e., that it is believed to be necessary to discern efficacy, should be discussed in the informed consent document.

- In addition to describing that randomization will be used to determine which subjects receive the active agent, the informed consent document should discuss the fact that two different doses of the study agent will be used and the rationale for them.

- The discussion in the informed consent document of the risks of the cardiac catherization procedure should be more complete and explicit and, to the extent possible, include quantitative data. In addition to other risks, this section should include a discussion of the risk of contrast-induced nephropathy from cardiac catherization along with the measures that will be taken to mitigate the risk.

G. Committee Motion 2

Dr. Federoff summarized a variety of preclinical, clinical, and consent form issues, which will be included in the letter to the investigators and the sponsor as expressing the comments and concerns of the RAC. The vote was 14 in favor, 0 opposed, 1 abstention, and 0 recusals.

IV. Gene Therapy: Opportunities and Challenges—The Next Decade

Speaker: Theodore C. Friedmann, M.D., University of California, San Diego

Dr. Friedmann provided a retrospective look at gene therapy, including current and developing concepts and methods of gene therapy and long-range future potential, challenges, and dangers. He offered his view of the evolving role of the RAC and how the RAC could further enhance the current gene therapy research effort through its oversight role, policy role, and an expanded educational role.

The conventional wisdom on gene therapy is that the concept itself, the technology, and the application to clinical issues are unproven. Gene therapy has been assessed as a field that has produced SAEs without convincing therapeutic benefits, and that is taking a long time to develop.

In 1995, with the publication of several papers describing the clinical results of studies dealing with cystic fibrosis, adenosine deaminase-deficient severe combined immunodeficiency (ADA-SCID), and glioblastoma, there was profound disappointment because the studies showed very little robust transgene expression. Although the potential was acknowledged, no therapeutic benefits were seen, and the technology of transferring and maintaining transgene expression was not well developed. At that time and in response to reports from two advisory committees, then-NIH Director Harold Varmus suggested a rethinking of the basic science and a retooling of the clinical studies in the gene transfer field. Starting in 1988 with the first gene transfer protocol, Steven Rosenberg's marking study, there was an increase in the number of protocols that submitted to the RAC, indicating a persistent optimistic view about the potential of the gene transfer field. This changed when a research participant, Jesse Gelsinger, died in 2001, a few days after being infused with an adenoviral ornithine transcarbamylase vector.

In 2002 Alain Fischer and colleagues in Paris reported a sustained correction and immunological reconstitution of children with X-linked severe combined immunodeficiency (X-SCID) followed by clinical improvement, an unequivocal demonstration of the therapeutic effect of the delivered transgene; the effect has persisted for four years. However, the cost of this therapeutic benefit is that, to date, four of the participants in the Paris study have developed T-cell leukemia, resulting in 1 death. Because of the benefits observed in the Paris study, another X-SCID study in London, and an ADA-SCID study in Milan, "gene transfer research" could rightfully be termed "gene therapy," at least in relation to immunodeficiency diseases.

Another area of apparent clinical efficacy relates to cancer—the approach of directly injecting adenovirus-p53 (Gendicine) into tumors. In single-mode treatment and in combined treatments, the research participants seem to be showing responses to the combined treatments of surgery, chemotherapy, and radiation plus direct injection of Gendicine into the tumor. Some clinical efficacy has also been observed in some immunotherapy studies. Another area of promise is the gene transfer for Leber's congenital amaurosis based on the benefit in the dog model. Other impressive emerging technologies include RNA interference and zinc fingers coupled to functional domains.

In summary, in 17 years of clinical application of gene transfer, approximately 800 protocols have been reviewed by the RAC and the FDA. Vectors and gene transfer methods have improved. It is now known that gene regulation needs to be attended to, and in the course of these studies, much has been learned about pharmacology/toxicology and safety data. In addition, major AEs have occurred. That gene transfer can be an effective therapy has been proven unambiguously but only for a small number of diseases, particularly the immunodeficiencies.

Regarding the concern that gene therapy is taking too long to develop as a therapeutic field, Dr. Friedmann noted that bone marrow transplantation, which currently plays a central role in medicine, went through an initial period in which only about 1 percent of patients receiving bone marrow transplantation survived. Cancer chemotherapy experienced a similar development period, with an initial survival rate of about 8 percent of children with T-cell leukemia. Both of these developments are reminiscent of what is being experienced now in gene therapy, and a 20- or 30-year development timespan is not unusual.

Dr. Friedmann suggested that the RAC could continue to enhance the gene therapy effort through both its oversight function and an expanded educational role. The RAC has been the primary public voice for the field of gene therapy. The RAC's well-planned educational and policy roles have involved a number of safety symposia since 2000, dealing with topics such as adenoviral vectors and X-SCID. The RAC has sponsored two policy conferences; this is an area that the RAC might want to build on. The RAC also has established a working group (WG) to examine the informed consent problems seen in protocols; that WG developed a set of standards for the informed consent process in gene transfer clinical trials. Another area which may benefit from a similar effort by the RAC is the optimal design of clinical studies. The Genetic Modification Clinical Research Information System (GeMCRIS) function is extremely important but underutilized at present.

Future policy issues for the RAC's consideration may include the potential reemergence of fetal applications for gene therapy and potential nontherapeutic applications of gene transfer, also known as enhancement effects. For the longer term, Dr. Friedmann suggested that germline modification will become more tempting as gene transfer technology develops, which also will require the development of genetics-based social and public policy.

V. Gene Transfer Safety Assessment Board (GTSAB) Report

RAC Reviewers: Drs. Albelda, Federoff, and Heslop

Dr. Albelda discussed the amendments received during the 3-month reporting period October 11, 2006, through January 17, 2007. During this period, the OBA received 17 protocol submissions, of which 15 were not selected for public review at this RAC meeting. Of those 15 protocols not selected, 14 were for cancer, and 1 was for diabetic peripheral neuropathy; 6 used a plasmid vector, 5 used a retroviral vector, 2 used a pox viral vector, and 1 each used an adenoviral vector and a herpesviral vector.

During the reporting period, 129 amendments were received by the OBA, including 19 protocol design modifications, 46 annual reports, and 8 responses to *Appendix M-I-C-1* of the *NIH Guidelines*. Three amendments were discussed:

- In Protocol #0504-703, A Phase I, Safety, Dose-Escalating Study of MultiGeneAngio in Patients with Peripheral Arterial Disease, which was discussed at the June 2005 RAC meeting, the sponsoring company agreed with the suggestion that preclinical studies should be conducted using the same product that would be used for the clinical trial. The investigators provided the results from preclinical studies that examined blood perfusion and blood flow in nonhuman animals that were injected with vehicle or marker gene. Biodistribution and persistence of the delivered cells were analyzed by monitoring viral deoxyribonucleic acid (DNA) and transgene mRNA levels, and the suggested additional statistical analyses were carried out. The clinical protocol was reworded to clearly indicate that individuals who had participated within the previous 30 days would be excluded, the principal investigator (PI) would make enrollment decisions, and

a clinician not involved in the study would discuss the options available to potential participants. The investigators also provided the RAC with more long-term followup plans for their protocol.

- Protocol #0604-769, A Phase I, Randomized, Placebo-Controlled, Open-Label, Cross-Over Safety and Pharmacodynamic Study of BHT-3021 in Subjects with Recent Onset Type 1 Diabetes Mellitus, was discussed at the June 2006 RAC meeting by representatives of Bayhill Therapeutics, Inc. In response to concerns regarding immunogenetic differences leading to variable responses to the vaccine, the investigators indicated that human leukocyte antigen types would be determined. Participants will be followed for 3½ years regardless of whether they receive study agent or placebo. After nine months of followup, individuals who received placebo would be eligible to cross over to the study. Changes to the informed consent document, as suggested by the RAC, have been made.

- Protocol #0607-788, A Multicenter, Randomized, Double-Blind, Sham Surgery-Controlled Study of CERE-120 (Adeno-Associated Virus Serotype 2 [AAV2]-Neurturin [NTN]) to Assess the Efficacy and Safety of Bilateral Intraputamenal Delivery in Subjects with Idiopathic Parkinson's Disease, was sponsored by Ceregene, Inc., and discussed at the September 2006 RAC meeting. In response to concerns regarding the sham surgery control group and overall sample size, the investigators indicated that analysis of the Phase I study involving the administration of CERE-120 had suggested that a 40-percent reduction in symptoms was occurring; however, because of the strong placebo effect, the investigators have elected to continue the sham surgery control arm. A statistical analysis was provided to indicate that the sham control group of 17 was sufficient to provide 90-percent power to detect a 25-percent difference. The investigators also agreed with the RAC's suggestions about collection and storage of peripheral blood mononuclear cells and made several changes to the informed consent document based on the RAC's recommendations. The investigators chose not to pursue the RAC's suggestion of having two informed consent documents, one with the positron emission tomography protocol and one without.

Dr. Heslop discussed the AEs reported during this period. A total of 171 AEs were reported from 36 trials during this period, of which 38 AEs from 14 trials were deemed possibly related to the experimental process or product. She briefly discussed 4 AEs from 4 trials, 2 of which resulted in unexpected participant deaths that were initially determined to be possibly related to the gene product:

- Protocol #0604-772, A Phase II Study of Direct Tumor Injection of TNFerade™ Followed by KLH-Pulsed Autologous Dendritic Cells in Patients with Unresectable Pancreatic Cancer, reported an unexpected death. In this trial, the vector was injected into the pancreatic tumor followed by irradiation and intratumoral injection of an autologous dendritic cell vaccine. The research participant was found dead at home less than 1 week after receiving a second dose of the gene product and several days after receiving the dendritic cell vaccine. Jurisdiction of the case was given to the medical examiner, but despite the efforts of the PI to obtain an autopsy, it was not done, so the cause of death remains unknown. There was no history of coronary artery disease, and the participant had not complained of any symptoms leading up to the event.

- Protocol #0608-801, A Phase II Trial Using GM-CSF-Producing and CD40-L-Expressing Bystander Cell Line (GM.CD40L) in the Formulation of Allogeneic Tumor Cell-Based Vaccines in Combination with ATRA and Cyclophosphamide for Patients with Stage IV Adenocarcinoma of the Lung, also reported an unexpected death. The elderly participant, who had metastatic lung cancer and known malignant pulmonary effusion, received the first vaccine and started all-trans retinoic acid. About 1 week later the participant was admitted to the hospital with weakness, fatigue, and shortness of breath and was diagnosed with pneumonia and possible sepsis. The participant had a complicated clinical course and died in the hospital with a diagnosis of acute respiratory distress syndrome. No autopsy was performed. Initially, the PI could not exclude the possibility that the gene product was a contributing factor, but after receiving negative results for serum cytokine levels, the investigators concluded that the death was unlikely to be related to the

gene product and more likely to be related to the participant's underlying condition and comorbidity.

- In Protocol #0510-729, A Phase I Clinical Trial of Repeated-Dose Intrapleural Adenoviral-Mediated Interferon-β Gene Transfer for Pleural Malignancies, an SAE involving a pericardial effusion was reported. In this study, the vector was given into the pleural space by catheter, and this participant's pleural effusion was on the left side. Nine days after receiving the second dose of the study agent, the participant was admitted to the hospital with symptomatic pericardial effusion requiring drainage. The participant made a recovery, and it was noted that this person had had a known pericardial effusion on enrollment in the study. The investigators conducted extensive studies on participants in this trial and in Protocol #0204-531, a similar protocol using the same investigational agent. The studies looked for recombinant adenovirus in swabs from the chest wall, pleural fluid, and blood samples. No RCA was found, but positive DNA PCR for adenoviral vector was found in most participants' pleural fluid for up to 4 weeks. In response to this SAE, Protocol #0510-729 was amended to exclude participants with preexisting pericardial effusions. Of note, the decision to screen for and exclude participants with pericardial effusions also may be applicable to other protocols.

- Protocol #0407-661, A Phase II, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Dose-Selection Study of Ad2/Hypoxia Inducible Factor (HIF)-1 α/VP16 in Patients with Intermittent Claudication, reported SAEs that involved the development of malignancies, predominantly prostate cancer. Given that the trial is blinded, it is not possible to state whether participants identified in these SAEs received the gene product. In 2001 the RAC proposed a recommendation that screening for cancer be done in all participants enrolled in such studies. Protocol #0407-661 now has screening procedures in place and requires that all participants have a full physical exam with laboratory work and be current with the age-appropriate cancer screening for breast, cervical, colon, and prostate cancers. Lung cancer screening is done by x-ray. Ongoing screening for cancer continues during the protocol. In addition, the trial excludes certain participants who are at high risk for malignancy.

Dr. Heslop noted that the GTSAB continues to track all malignancies reported from gene transfer trials involving growth factors. However, at this time, the available data do not allow any conclusion to be drawn about the added risk, if any, that growth factors present for developing a malignancy.

The RAC has reviewed a number of adverse events on trials that used the adenoviral vector that expresses tumor necrosis factor (TNF) alpha, in addition to the death of the subject discussed earlier. Most of these trials do not include injection with a dendritic cell vaccine. As stated earlier, because of the potential prothrombotic nature of the vector, these trials typically include a screening process for thrombosis and some ongoing monitoring. Nonetheless, some adverse events have been reported to OBA involving deep vein thrombosis in subjects who have received this adenoviral vector that leads to the expression of TNF alpha. While the majority of these SAEs is attributed by the investigator and sponsor to the underlying disease, one of the difficulties in evaluating whether the TNF expressing adenoviral vector could be a contributing factor is that many malignancies lead to a prothrombotic state. For example, in some reports, the incidence of thromboembolic disease in patients with pancreatic cancer is between 17-50%. Somewhat reassuring is an interim analysis in one of the larger trials, protocol 0204-530, which uses this investigational agent for pancreatic cancer. This trial is a placebo controlled trial. Analysis of the first 40 subjects (25 subjects in the gene transfer group and 15 subjects in the standard of care group) did not reveal an increased risk of thrombosis in subjects treated with the adenoviral vector containing the TNF alpha gene. The sponsor of this trial continues to monitor this closely and has an ongoing data safety management board plan.

In order to explore the link between malignancy and thrombosis further, Dr. Jay Lozier, a senior clinician from the NIH Clinical Center, Department of Laboratory Medicine in the Division of Hematology was invited to present on the topic. Prior to coming to NIH, Dr. Lozier was a senior staff fellow at the FDA Center for Biologics Evaluation and Review. He also served as a Special Expert on the Gene Technology Section, Clinical Gene therapy Branch of the National Human Genome Research Institute.

Dr. Lozier discussed the current understanding about the prothrombotic state of malignancy and its implication for therapies such as TNF which use thrombosis as an anti-tumor mechanism.

VI. Thrombosis and Malignancy: Implications for Therapy

Speaker: Jay Lozier, M.D., Ph.D., Warren Grant Magnuson Clinical Center, NIH

Dr. Lozier described hemostasis as the balanced process of clot formation (coagulation) and its gradual lysis and remodeling (fibrinolysis). He reviewed the role of platelets, the coagulation cascade, and endothelial cells in coagulation and the anti-coagulant proteins in fibrinolysis. Blood coagulation without fibrinolysis results in pathologic thrombosis and if blood coagulation proceeds beyond the local injury disseminated intravascular coagulation (DIC) occurs.

It has long been recognized that cancer in general—and pancreatic cancer in particular—is associated with pathologic thrombosis. Trousseau's syndrome is thrombophlebitis associated with visceral cancers, especially pancreatic cancer; other epithelial or nonepithelial malignancies, such as gliomas, also may predispose to thrombosis. Thrombosis can precede the diagnosis of pancreatic cancer and is a dire prognosticating factor. Chemotherapy increases risk, perhaps from the chemotherapy itself but also possibly due to indwelling catheters, which can promote thrombosis in the circulating blood. The pathophysiology of thrombosis with malignancy typically involves the shedding of microvesicles that express tissue factor from tumor cells and angiogenesis-promoting factors that are critical to the tumor's metastatic potential. Thrombosis associated with malignancy is often treatable with heparin anticoagulation, but warfarin anticoagulation is typically less successful; this difference may be due to heparin's extra anti-inflammatory effects or its antiangiogenic effects in addition to its anticoagulant properties.

TNF-α is one of the early primary inflammatory cytokines. Studies have been conducted in which TNF-α was injected into the skin of normal volunteers, leading within 24 hours to increased tissue factor expression, reduced tissue factor pathway inhibitor, and thrombomodulin. This result indicates a local increase in procoagulant proteins and a decrease in anticoagulant proteins, which could be the basis for the long-known correlation between inflammation and the increased risk for thrombosis.

Adenoviruses are toxic to human endothelial cells, and Dr. Lozier and colleagues have shown that systemic delivery of adenoviral vectors in nonhuman primates has adverse effects on anticoagulant proteins and may result in consumption of fibrinogen and platelets.

From the information and data presented, Dr. Lozier concluded that:

- Patients with pancreatic cancer have a very high baseline risk for thrombosis (compared with the general population).
- The systemic inflammatory and procoagulant effects of adenoviral vectors may contribute to the risk for thrombosis.
- Local TNF-α transgene expression may contribute to thrombosis risk.
- Prophylactic measures against thrombosis (heparin anticoagulation) in the setting of pancreatic cancer may be useful.
- Measures to monitor/detect incipient thrombosis are not proven or validated in this setting but may be reasonable scientific queries.
- Screening for common polymorphisms in coagulation/anticoagulation may uncover factors that increase thrombosis risk.

A. RAC Discussion

Dr. Ertl noted that while the use of heparin would reduce the risk of thrombosis, heparin also may interact with viral vectors used in gene transfer (e.g, AAV vectors binding heparin sulfate). Dr. Lozier responded that further study is needed; however, prophylaxis should resume after gene transfer. Dr. Federoff asked about the use of low-molecular-weight heparin producing optimal anticoagulation. Dr. Kirchhoff raised the possibility that intratumoral injection of adenoviral vectors could cause thrombosis in the tumor (one of the potentially desirable features of gene transfer).

VII. Human Cancer Immunotherapy Using Genetically Modified Autologous Lymphocytes

Speaker: Steven A. Rosenberg, M.D., Ph.D., NCI, NIH

Dr. S. Rosenberg presented the recent efforts to develop effective immunotherapies for the treatment of patients with metastatic cancer and talked about how genetic manipulations may help extend some effective immunotherapies to a wide variety of patients with melanoma and other common cancers. He discussed the three main approaches to cancer immunotherapy: (1) nonspecific stimulation of immune reactions (stimulating effector cells and inhibiting regulatory cells), (2) active immunization to enhance antitumor reactions (cancer vaccines), and (3) passive transfer of activated immune cells with antitumor activity (adoptive immunotherapy); of these, passive transfer has been the most successful.

In the search for immune cells that could recognize cancer antigens, tumor infiltrating lymphocytes (TIL) were identified. TIL are immune cells that infiltrate into the stroma of growing tumors. TIL can recognize autologous cancer antigens based on assays of specific lysis or specific cytokine release when cocultured with cancer cells. The advantages of cell transfer therapy include the abilities to administer large numbers of highly selected cells with high avidity for tumor antigens, administer cells activated *ex vivo* to exhibit antitumor effector function, and manipulate the host prior to cell transfer to provide an altered environment for transferred cells.

Dr. S. Rosenberg described some of the early melanoma studies. The conclusions from these studies included that adoptive transfer of activated anti-tumor T cells can mediate the objective regression of cancer in 50% of patients with metastatic melanoma. However, TIL can only be generated in approximately 50% of melanoma patients and rarely in patients with other cancer types.

Currently efforts are concentrating on using genetic manipulations for improving the *in vivo* survival of the transferred cells, providing higher affinity T cell receptors, and extending cell transfer to patients with other epithelial cancers. Efforts included introducing interleukin genes or T cell receptor genes specific for tumor antigens into TIL. Phage display techniques can be used to generate high-affinity T-cell receptors (TCRs) that recognize tumor antigens in a CD8-independent manner. Substitution of mouse constant regions into human TCR may increase the expression and function of transduced antitumor TCR.

After an extensive discussion of several relevant protocols and a presentation of encouraging case studies, Dr. S. Rosenberg summarized the current efforts to improve cell transfer therapy through methods of host modification and lymphocyte modification by gene transfer. Host modification methods include increasing preparative lymphodepletion by adding whole-body irradiation and administering a vaccine encoding the antigen recognized by the transferred T cells. The goals of lymphocyte modification by gene transfer include improving the *in vivo* survival of the transferred cells, providing higher affinity TCRs, and extending cell transfer therapy to patients with common epithelial cancers.

VIII. Discussion of Human Gene Transfer Protocol #0701-827: Phase I or Phase I/II Single-Center Trial of Gene Transfer for Recessive Dystrophic Epidermolysis Bullosa

Principal Investigator: Alfred T. Lane, M.D., Stanford University School of Medicine

Additional Presenters:	Paul A. Khavari, M.D., Ph.D.; M. Peter Marinkovich, M.D.; Zurab Siprashvili, Ph.D.; Stanford University School of Medicine
RAC Reviewers:	Drs. Heslop, Kodish, and N. Rosenberg
Ad hoc Reviewer:	Elena Pope, M.D., FRCPC, The Hospital for Sick Children and University of Toronto

A. Protocol Summary

Recessive dystrophic epidermolysis bullosa (RDEB) is one of several inherited, blistering skin diseases. Children with this condition are born lacking normal type VII collagen. Type VII collagen is a protein that anchors the outer layer of the skin (epidermis) to the inner layer (dermis). If type VII collagen is absent or does not function correctly, the epidermis easily separates from the dermis, causing blisters and wounds on skin or mucous membranes. Life expectancy is short due to early death from infection, organ failure, or squamous cell carcinoma (SCC) associated with complications of their chronic wounds. Current therapy for RDEB consists only of palliative wound care and pain control; no therapies alter the course or severity of the disease.

In studies of immune deficient mice, genetically corrected keratinocytes or fibroblasts have corrected human EB skin tissue grafts. In this study, human RDEB research participants will receive grafts of autologous keratinocytes transduced with a retroviral vector, pLZRSE-Col7A1, expressing type VII collagen to determine whether the grafts will provide long term healing of wounds that previously would never heal. Between two and ten adult participants with RDEB will be enrolled in the trial. The type VII collagen expressing grafts will be grown into epithelial sheets which will be placed on non-healing wounds on the subject's trunk. Two to four 3- by 3-inch grafts will be used in a single grafting session. The participants will undergo multiple skin biopsies and evaluations and be followed for their lifetime.

The endpoint of the study is detectable expression of type VII collagen at the basement membrane of grafted wounds, expression of type VII collagen in the grafted keratinocytes and presence of anchoring fibrils.

B. Written Reviews by RAC Members

Ten RAC members voted for in-depth review and public discussion of the protocol. Key issues included safety concerns about the cancer-causing potential of retroviral vectors being heightened by the greater risk for skin cancer that RDEB patients experience, the risk of developing autoimmunity to the transgene, and the need for additional discussion of vector production and risks to participants.

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

Dr. Heslop asked the investigators to clarify how many retroviral copies would be present in each target cell and requested information about the usual timeframe between transduction and completion of the required expansion. She also requested discussion of the risk of oncogenesis in the proposed participant population and the risks of biopsy, given the participants' risks for poor healing and infection. Dr. Heslop asked the investigators to clarify whether they plan to expand this proposed trial to include children in the future and what the corresponding criteria would be for extending this study to pediatric participants. She also asked for discussion about how the patient ombudsman will be chosen.

Dr. Kodish requested that the investigators remove language alluding to consent involving a surrogate decisionmaker if no participants in this protocol will be younger than 18 years of age. He asked for clarification and additional detail about the role of the ombudsman who will act as a patient care representative and asked that descriptions of this individual found in various locations in the protocol be made consistent. Dr. Kodish asked the investigators whether they anticipate that the gene transfer procedure would result in an incremental increase in the risk of sepsis over that associated with the underlying disease; if so, he suggested that the investigators should note that risk in the informed consent

document. He also asked for clarification of any future involvement of children in this protocol which may require separate RAC and institutional review board review.

Dr. N. Rosenberg asked the multiplicity of infection that will be used for the gene transfer and clarification of the number of copies of retrovirus per cell that will be present. She also asked the frequency with which cultures may be expected to express greater than 100 percent of the normal level of type VII collagen and the potential for immune side effects that might result from keratinocyte cultures that express as much as 50 times more type VII collagen than wild-type cells. She asked the relative risks of developing epidermolysis bullosa acquisita in participants who are N-terminal fragment of collagen negative (NC1-) compared with the risk of developing SCC in participants who express NC1+. She also asked whether biopsies might increase the risk of infection, and whether biopsy or the engraftment procedure could lead to increased inflammation that might increase the risk of developing SCC. She also requested clarification regarding the criteria to be used to determine whether the study will involve two participants or more than two participants.

Dr. Pope was unable to be present via teleconference, so Dr. Federoff summarized her review. She suggested adding to the exclusion criteria individuals with evidence of local or systemic infection at the time of gene transfer, individuals with a prior history of SCC, and individuals showing evidence of SCC at screening or at the time of gene transfer, irrespective of the site of involvement. Dr. Pope also suggested adding a protocol for wound bed preparation for gene transfer, a combination of topical antibiotics or antibacterial dressings and systemic antibiotics for a few weeks before grafting. She noted that doing so would minimize the chances of gene transfer failure resulting from infection.

C. RAC Discussion

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

- Dr. N. Rosenberg asked the investigators to speculate on the model by which the NC1 domain contributes to the development of SCC.

- Dr. N. Rosenberg asked for any information that would allow the investigators to estimate a difference in efficacy of the grafting procedure or other parts of the protocol that relate to the participant's age, particularly older children compared with adults.

- Dr. Vile requested information about the expected duration of gene expression.

- Noting that keratinocytes must be dividing to be transduced with this vector, Dr. Vile asked what eventually stops them from dividing.

- Dr. Vile asked whether a knockout mouse model could be used to model blistering.

- Dr. Dewhurst asked about the feasibility of a total body skin graft on a young infant and whether that was the investigators' ultimate goal.

- Dr. Weber requested that the investigators add a table of events and algorithms to the informed consent document.

- Dr. Flint requested clarification of how many adults the investigators intend to enroll and asked about the criteria the investigators would use to determine the appropriateness of expanding the participant population to include children.

- Dr. Ertl inquired about whether the T cells would reject a graft onto an inflamed wound. Because graft rejection normally occurs through T cells, not through antibodies, she requested that the investigators add to the protocol the statement that a T-cell-mediated reaction against the engrafted cells would be a reason to reassess the clinical trial.

- Dr. Kirchhoff asked about the percentage of RDEB patients who survive to adulthood. He expressed concern about whether the adults who survive are special in some way and not representative of the larger group of patients with the disease.

- Dr. Wei asked the investigators to describe how they would calculate the risk-benefit ratio with only two research participants.

- Dr. Kodish encouraged the investigators to consider enrolling children no younger than 10 or 12 years, even though the age of assent in California would allow them to enroll children as young as 7 years, thus considering assent ethically as well as legally.

- Several RAC members discussed with the investigators whether they should submit a new protocol or just an amendment to the current protocol at such time as they are ready to include children in this clinical trial. The RAC discussed the need for the investigators to consider the type of data, including number of adult participants and length of follow-up study, needed to guide a decision to move into a pediatric population of participants.

D. Investigator Response

Dr. Lane explained that the investigators are seeking guidance from the FDA and the RAC regarding the plans to enroll children. Ideally any treatment should start in infancy to minimize the pain, wounds and scars that patients develop. Many RDEB patients do not survive to adulthood and those who survive to be older than 18 years of age may be NC1- because the NC1+ patients may be dying with SCC. The investigators propose to dose two adults and evaluate at 6 weeks, 12 weeks, and 6 months. If the grafts are successful in two adults, the investigators propose to move down to the age of assent, which is 7 to 17 years of age in California, for the next phase of the protocol. The question has been submitted to the FDA regarding how many children between 7 and 17 years of age should participate in this protocol before the investigators would be allowed to enroll research participants younger than 7 years of age.

Dr. Lane stated that the percentage of RDEB patients who survive to adulthood is unknown. The investigators' practice includes 6 RDEB patients who are older than 18 years and approximately 30 children with RDEB. One of the six adult patients is NC1-; the others are untested. Dr. Lane expressed concern that the RDEB patients who are NC1- perhaps survive because they do not develop SCC earlier in life. Many of the RDEB children die between the ages of 7 and 10 years, or they die as neonates because of the severity of the disease.

The ombudsman role would be filled by Dr. Mildred Cho, PhD., associate director of the Stanford Center for Biomedical Ethics. She will act as an advocate for the research participants. She will have access to research data and communicate directly with the Data Safety Monitoring Board but would not be a member.

The gene transfer procedure is not expected to increase the risk of sepsis as RDEB patients are already at high risk due to the large areas of open wounds.

For the gene transfer, the moiety of infection (MOI) is anticipated to be 10 with two genome copies/cell. As determined by western blot, all the transduced keratinocytes expressed > 100% of the normal level of type VII collagen. The larger amounts of protein can induce tolerance or precipitate an autoimmune response. Because the NC1 domain of type VII collagen is the major immunogenic domain, only subjects who are NC1+ will be enrolled. The subjects will be monitored for autoantibody production using ELISA assays for purified type VII collagen, NC1 domain. If any signs of autoimmunity are observed, subjects will be treated and the grafts removed. Studies have shown that ectopic over-expression (> 50 fold) of type VII collagen has no apparent effect on skin differentiation and the collagen assembles in a biologically active form.

Introduction of the full-length type VII collagen protein into subjects null for Col7A1 expression may increase the risk of raising auto-antibodies and development of EBA. Subjects who are NC1+ will be enrolled because they are likely to have already developed immune tolerance. While increased risk of SSC in NC1+ subjects is not expected, the grafts will be monitored for neoplasia and removed if malignancy is detected.

Skin biopsies normally are associated with a 2% risk of infection; however, this may be higher in RDEB patients because of the colonization of their skin wounds with pathogens. Patients are routinely biopsied as infants to confirm the EB diagnosis and as adults for SCC diagnosis. Subjects will be informed of the small increased risk of infection.

Regarding Dr. Pope's suggestions for exclusion criteria, Dr. Lane agreed that potential participants with active infections would not be grafted during the time of the infection. The participants may need to arrive two weeks prior to gene transfer to allow time to prepare the wounds for grafting. Participants with SSC may be included because adult participants may have undiagnosed SSC and excluding potential participants with SCC may make it difficult to identify participants at the age of 19 or 20 years who do not have SCC. Biopsies are exceedingly painful for RDEB patients, and most participants would likely refuse to be biopsied. However, participants with metastatic SCC to the lymph nodes or other organs will be excluded. Should SCC develop after grafting, genomic analysis will be performed on tumor cells to detect vector sequence.

The investigators are developing a protocol for wound bed preparation similar to Dr. Pope's suggestions. They are collaborating with Genzyme on a potential protocol using Epicel™.

Dr. Khavari explained that, as a result of several experiments the investigators have performed, they do not believe that the NC1 domain is an oncogene but rather that it enables oncogenic invasion if oncogenic networks have already been engaged.

Regarding a participant's age, Dr. Lane stated that individuals who receive the graft will need to be fairly immobilized; the grafting technique is similar to that used for burn patients, and the special dressings that cover the graft remain in place for several days. Given this situation, adults will be more cooperative at immobilization than children. However, as far as the health of the individual, as long as the participant has good nutrition and a clean wound, the investigators expect the protocol to be equally as successful in a young adult, an older adult, a young child, or an infant.

Regarding the length of gene expression, Dr. Siprashvili explained that all of the data are from human skin regenerated on SCID mice. Those data show gene expression—and thus skin regeneration—to 8½ months.

Noting that the skin is a renewable tissue, Drs. Khavari and Marinkovich explained that the keratinocytes achieving contact inhibition signals a mature epidermis, resulting in a decrease in cell division. The investigators have examined the kinetics of epidermal turnover in homeostasis, and approximately every 28 to 35 days the entire epidermis goes through a full self-renewal cycle from progenitor stem cells in the basal layer of the epidermis. That process leads to a number of proliferating cells that are in balance with the cells that undergo programmed cell death.

Dr. Siprashvili explained that a knockout mouse model is available. However, if the mouse is heterozygous, it is viable for a full lifespan but has normal skin, and if the mouse is homozygous in deletion, then its lifespan is only 2 to 3 weeks.

Regarding the extent of grafting if this procedure should become a therapy, Dr. Lane noted that RDEB patients experience significant, constant pain and suffering. Certain sites on the body are a continuing problem—hands, elbows, knees, and the back—and RDEB patients have severe major itching at these sites, resulting in scratching and inducing damage. These patients have learned how to protect their skin in other sites by wearing dressings all day, so grafting the whole body may not be necessary. Other

secondary sites for grafting include mucous membranes, esophagus, urethra, and rectum, all of which are areas of trauma and injury.

In response to questions about the possibility of systemic administration of either cells or protein, Dr. Khavari explained that the investigators have tried to undertake studies that use injected protein to reproduce the research that has been done elsewhere, but those studies have not been successful. The use of grafting as proposed in this protocol comprises techniques that have worked well for burn grafting. The other advantage, if there were a systemic hypersensitivity reaction to the protein and infused cells could not be recovered, is that keratinocytes will remain locally in the skin, will not travel throughout the body, and thus can be removed easily.

Dr. Lane explained that the risk-benefit ratio would be calculated by analyzing results for the two research participants over a period of time to determine whether they have developed autoantibodies, whether the grafted skin looks as normal as possible, and whether the grafted skin has developed SCC. Biopsies will be performed, and inflammation and blistering caused by an antibody-mediated immune response will be visually apparent. Success will be defined as the presence of type VII collagen and the presence of what appears to be somewhat normal skin on a scarred surface.

E. Public Comment

Dr. Kevin A. Prohaska, OHRP, asked for information as to why the proposed procedure might work better in children. He noted that the informed consent document was confusing at some locations and that the investigators should consider making the ombudsman available to participants at all times. Dr. Prohaska reminded the investigators that continuing to contact participants who withdraw is not allowed.

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 protocol proposes to screen prospective research participants for production of the N-terminal fragment of collagen (NC1+) because NC1+ participants have an increased risk of SCC. The exact mechanism by which NC1+ contributes to this risk is not known. The investigators should consider additional preclinical studies of potential mechanisms of oncogenesis. In particular, any interaction of the overproduced, secreted transgene product with the *ras* oncogenic network should be investigated.

- The protocol involves the placement of transduced keratinocytes that will significantly overproduce collagen type VII into wounds. Since overproduction of collagen type VII may induce a T-cell response, studies in an appropriate animal model should be considered.

Clinical/Trial Design Issues

- While the transduced keratinocytes are known to over-produce collagen type VII, the level of over-production of collagen type VII in the grafts is not known. The levels in the grafts should be measured because the over-production could contribute to any autoimmune reactions that might be observed. In addition, given the prediction that the grafts will also over-produce collagen VII, the research participants should be closely monitored for autoimmune reactions.

- If any subject experiences graft rejection, appropriate studies to determine the role of a T cell-mediated immune response should be conducted.

- The mutations in the collagen type VII gene of prospective research participants should be analyzed to determine whether there are any significant differences between potential adult and

child research participants (e.g., selection of specific mutations in research participants surviving to adulthood) as this information may be useful for subject selection.

- The current protocol proposes enrolling two adults prior to enrolling children. It is not clear that safety data from two adult subjects will be sufficient to justify proceeding to pediatric subjects. The appropriateness of this plan should be reconsidered. Prior to proceeding to enroll children, the number of adult subjects and the length of time they are followed needs to be considered.

Ethical/Legal/Social Issues

- Although adult patients with RDEB often rely parents or other caregivers for assistance with the activities of daily living, it is important to ensure that the patients themselves are consenting to the research, not their caregivers.

- The informed consent document refers to both a medical ethicist and an ombudsman/ombudsperson who is to act as a patient care representative. Since the word ombudsman commonly refers to a person who settles disputes, another term, such as research subject advocate, may be more appropriate. In any case, one term should be used and used consistently. In addition, it would be helpful if the advocate were also available to the participants after the consent process is completed.

- Because of the variation in the subjects' capabilities, particularly given that children may be enrolled, the consent process will need to accommodate subjects who are capable of consenting themselves, pediatric subjects who are capable of assent but require a surrogate or legally authorized representative; and adult or pediatric subjects who cannot participate in the process at all and require surrogate decision makers. If the decision is made to move to children, older children, who have the capacity to give informed assent, should be considered before younger children.

- The informed consent document should be modified in the following ways:

    - The use of multiple consents for the various procedures is confusing. It may be helpful to clarify what is being consented to in each form.

    - The addition of a protocol algorithm and table of events to clarify the procedures may help enhance the clarity of the protocol.

    - A discussion of the risks associated with administration of anesthesia should be included.

    - Explicit descriptions of the preferred method and duration of birth control for female participants should be included.

    - A statement about whether birth control is required for male participants should be included.

    - The use of the term sterile to describe the procedures such as the biopsies is misleading. These are better characterized as aseptic procedures because the wounds are not sterile.

    - The statement that a benefit to participating in research includes access to therapy in the future is misleading and should be deleted. If the therapy is shown to be effective and is licensed, it will be accessible through clinical care.

    - Further guidance on crafting the informed consent for gene transfer research is available at http://www4.od.nih.gov/oba/rac/ic.

G. Committee Motion 3

Dr. Federoff summarized a variety of preclinical, clinical, and consent form issues, which will be included in the letter to the investigators and the sponsor as expressing the comments and concerns of the RAC. The vote was 15 in favor, 0 opposed, 0 abstentions, and 0 recusals.

IX. New Developments in X-SCID Gene Transfer

Moderators: Drs. Federoff and Friedmann
Speakers: Marina O'Reilly, Ph.D., OBA, OD, NIH; Jacqueline Corrigan-Curay, J.D., M.D., OBA, OD, NIH; Harry L. Malech, M.D., NIAID, NIH; Fabio Candotti, M.D., NHGRI, NIH; and Carolyn A. Wilson, Ph.D., FDA, DHHS

Dr. O'Reilly offered a brief review of the issues and the RAC's previous discussions. In December 2002, February 2003, and March 2005, the RAC reviewed the clinical and molecular data concerning three adverse events that occurred in a French study involving engraftment of a $CD34^+$ hematopoietic stem cell enriched, cell population transduced with a retroviral vector encoding the common gamma chain (γc) transmembrane protein subunit shared by receptors for Interleukins 2, 4, 7, 9, 15 and 21. The leukemias appear to share the common causative mechanism of insertional mutagenesis at or near oncogenes. The major goal of the symposia was to increase awareness in the scientific community and the public by providing comprehensive updates of the current US and international trials using gene transfer for SCID, including recently emerging safety data, retroviral integration and insertional mutagenesis research, and the use of bone marrow/stem cell transplantation as treatment for SCID. Based on the discussion, in 2005, the RAC made the following recommendations, which would be reviewed and potentially revised as new data becomes available.

- 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.

Dr. Corrigan-Curay discussed SAEs that have been reported in retroviral trials. The SAEs in retroviral studies had been reviewed in 2002 before the complete implementation of AE module of the genetic modification clinical research information system, commonly known as GeMCRIS. To update this report, GemCRIS was searched for any malignancies, leukemias, lymphomas, or myelodysplastic syndrome not consistent with disease process. In 2002, eight AEs were reviewed: four lymphomas, two myelodysplastic syndromes, one case of monoclonal lymphoproliferation, and one malignant glioma. Reanalysis using the GeMCRIS database resulted in capturing those same eight cases while also identifying four additional cases not yet reviewed: a peripheral nerve sheath tumor, rectal cancer, development of monosomy 7, and adenocarcinoma. From this search, she concluded that a small number of SAEs have occurred across multiple trials with retroviral vectors, including those transducing hematopoietic cells. Almost all of those cases have genetic/PCR or clinical evidence indicating that it is unlikely that the SAEs were related to use of the retroviral vectors. GeMCRIS helped augment initial queries from 2002; however, GeMCRIS covers only those trials registered with the OBA; therefore, likely does not capture all SAEs in gene transfer trials.

Dr. Malech described X-SCID as a profound lack of T and B cells due to a defect in the common gamma chain that affects interleukins 2, 4, 7, 9, 15, and 21. When available, the treatment of choice has been

bone marrow transplant from a matched sibling donor; however, most patients lack such a match and may receive a transplant from a parent. The limitations of transplant include the potential for graft vs. host disease, poor or no B cell engraftment, no NK cell repair and progressive decreases in the number and diversity of donor T cells. Dr. Malech detailed an NIH clinical trial of gene transfer as salvage treatment for older children with X-SCID. The participants had received transplants from parents as infants but did not achieve satisfactory immune reconstitution or subsequently had significant waning of immune function and loss of T cell diversity. He described the case histories of the three research participants. Results of the NIH clinical trial indicate no adverse effects of the gene therapy to date in the three preadolescents with X-SCID and analysis of retroviral insertion sites and TCR repertoire studies indicates polyclonality of transduced cells. Regarding efficacy, vector proviral levels were highest in T cells, present in B cells and natural killer cells, and lowest in myeloid cells. T-cell reconstitution, particularly CD4, was highest in participant #2 but did not reach normal numbers in any of the participants. As a result of the gene therapy in participant #2, an increase was observed in CD4 T cells (although not to normal levels), new naive T cells appeared, and new T-cell proliferative responses to *Candida albicans* were observed.

Dr. Candotti discussed the use of gene transfer with retroviral vectors for ADA-SCID. ADA deficiency makes up approximately 16 percent of all SCID cases. He reviewed the conventional treatments available and discussed in detail 10 gene transfer trials for ADA-SCID since 1990. In those trials, a total of 29 participants have been dosed, 26 of whom are infants. Of those treated, 12 participants have shown gene marking for 30 months or longer, and 12 participants showed clinical benefit (not necessarily the same individuals who showed gene marking). No lymphoproliferative complications have been observed. Gene transfer for ADA-SCID compared with X-SCID involves a similar retroviral vector integration pattern but a different outcome, different cooperation patterns for the two gene products, and technical differences between the gene therapy protocols.

Dr. Wilson presented the current FDA perspective on the use of retroviral vectors for the treatment of X-SCID and other clinical applications. She noted that the FDA acknowledges the risks associated with the use of retroviral vectors, which are primarily the risk of replication-competent retroviral production and the risk of insertional mutagenesis from the vector. The current FDA perspective on X-SCID clinical trials is that gamma retroviral vectors can be used in clinical trials to treat X-SCID under the following conditions: when individuals have failed previous hematopoietic stem cell/bone marrow transplantation and when no reasonable alternative therapies exist. Other clinical trials using retroviral vectors are being allowed to proceed, although the FDA acknowledges that risks still exist; however, if a retroviral vector-related malignancy were to develop in any other clinical trial, the FDA would reconvene its advisory committee. Dr. Wilson concluded by stating that the most recent SAE report from France does not change the FDA perspective on risks associated with retroviral vectors. Two guidance documents provide recommendations to sponsors to address risks to participants in retroviral vector-mediated clinical trials. She noted that a National Toxicology Program study is under way to assess a preclinical model to study the risks associated with retroviral vectors.

Dr. Friedmann concluded that there did not appear to be reasons to change the 2005 recommendations of the RAC. After the report of the third SAE, the recommendations were revisited with the conclusion that the risk:benefit assessment was not changed. There was not yet any evidence to conclude differently due to the fourth SAE. For now, the RAC should wait for the data on the vector insertions. Other questions, he believed would be interesting to pursue were the differences between the French and British trials, between the ADA and X-SCID trials, and the potential interaction between the gamma C transgene and LMO-2 or other oncogenes that may be targeted by insertional mutagenesis.

X. Closing Remarks and Adjournment/Dr. Federoff

Dr. Federoff noted that several RAC WGs have begun deliberations, including the Single-Use Exception WG, the Biosafety WG and the Clinical Trials WG. Progress will be presented at the June 2007 RAC meeting.

Dr. Federoff thanked the participants and adjourned the meeting at 5:20 p.m. on March 14, 2007.

[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.
Acting RAC Executive Secretary

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

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

Date: _____

_____
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Attachment III
Abbreviations and Acronyms

ADA-SCID	adenosine deaminase deficiency SCID
AE	adverse event
DHHS	U.S. Department of Health and Human Services
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
FDA	Food and Drug Administration, DHHS
GeMCRIS	Genetic Modification Clinical Research Information System
GTSAB	Gene Transfer Safety Assessment Board
HRT	hormone replacement therapy
NC1+	N-terminal fragment of collagen
NC1-	negative N-terminal fragment of collagen
NCI	National Cancer Institute, NIH
NHGRI	National Human Genome Research Institute, NIH
NIAID	National Institute of Allergy and Infectious Diseases, NIH
NIH	National Institutes of Health
NIH Guidelines	*NIH Guidelines for Research Involving Recombinant DNA Molecules*
OBA	Office of Biotechnology Activities, NIH
OD	Office of the Director, NIH
OHRP	Office for Human Research Protections, DHHS
PCR	polymerase chain reaction
RAC	Recombinant DNA Advisory Committee
RCA	replication-competent adenovirus
RDEB	recessive dystrophic epidermolysis bullosa
RNA	ribonucleic acid
SAE	serious adverse event
SCC	squamous cell carcinoma
TCR	T-cell receptor
TNFα	tumor necrosis factor alpha
VTE	venous thromboembolism
WG	working group
X-SCID	X-linked severe combined immunodeficiency