RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

December 13 and 15, 2000

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/documents1.htm>.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
RECOMBINANT DNA ADVISORY COMMITTEE
MINUTES OF MEETING[1]
December 13 & 15, 2000

The Recombinant DNA Advisory Committee (RAC) was convened for its 80th meeting at 8:30 a.m. on December 13, 2000 at the National Institutes of Health (NIH), Building 31, Sixth Floor, Conference Room 10, 9000 Rockville Pike, Bethesda, MD 20892. Dr. Claudia A. Mickelson (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public on December 13 from 8:30 a.m. until 5:20 p.m. and on December 15 from 8:30 a.m. until 5:10 p.m. The following individuals were present for all or part of the meeting.

Committee Members

C. Estuardo Aguilar-Cordova, Harvard Gene Therapy Initiative
Dale G. Ando, Cell Genesys
Xandra O. Breakefield, Massachusetts General Hospital
Louise T. Chow, University of Alabama, Birmingham
Theodore Friedmann, University of California, San Diego
Jon W. Gordon, Mount Sinai School of Medicine
Jay J. Greenblatt, National Cancer Institute, National Institutes of Health
Eric T. Juengst, Case Western Reserve University
Nancy M.P. King, University of North Carolina, Chapel Hill
Sue L. Levi-Pearl, Tourette's Syndrome Association
Ruth Macklin, Albert Einstein College of Medicine
M. Louise Markert, Duke University Medical Center
Claudia A. Mickelson, Massachusetts Institute of Technology

Executive Secretary

Amy P. Patterson, National Institutes of Health

Nonvoting/Agency Representatives

Jeffrey M. Cohen, Office for Human Research Protections
Philip Noguchi, Food and Drug Administration

Ad Hocs Reviewers
Nigel Mackman, Scripps Research Institute
Glen R. Nemerow, Scripps Research Institute
Jeffrey L. Platt, Mayo Clinic/Mayo Medical School
Stephen J. Russell, Mayo Clinic
Edith Tzeng, University of Pittsburgh Medical Center

Speakers

James D. Foss, Stellar Systems
Deborah Hurst, Chiron Corporation
Beth Hutchins, Canji, Inc.

[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.

Ann M. Pilaro, CBER, FDA
Stephanie L. Simek, CBER, FDA
Carolyn A. Wilson, CBER, FDA

National Institutes of Health Staff Members:

Jeff Ball, OBA
Steven Bauer, FDA
John Burklow, OD
Sarah Carr, OBA
Christine L. Densmore, NIAMS
Kelly Fennington, OBA
Robert Jambou, OBA
Richard A. Knazek, NCRR
Barbara McDonald, OBA
Marina O'Reilly, OBA
Alexander Rakowsky, OBA
Gene Rosenthal, OBA
Nava Sharver, NIAID
Michael H. Sayre, CSR
Thomas Shih, OBA
Sonia I. Skarlatos, NHLBI
Lana Skirboll, OSP, OD

Others

Approximately 60 individuals attended each day of this 2-day RAC meeting. A list of attendees appears in Attachment II.

I. Call to Order and Day One Opening Remarks/Dr. Mickelson

Dr. Mickelson, RAC Chair, called the meeting to order at 8:30 a.m. on December 13, 2000. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* was published in the *Federal Register* on October 2000 (65 FR 60328). Issues to be discussed by the RAC at this meeting included reviews of six gene transfer protocols, overview of the final timing action, summary of the U.S. Food and Drug Administration's (FDA's) guidance document on replication-competent retrovirus testing, overview of the current state of efforts to develop new generations of retroviral vectors, discussion of collaborative efforts to develop an adenoviral vector testing standard, data management report, status report on the NIH Office of Biotechnology Activity's (OBA) pilot database "Gene Modification Clinical Research Information System," status report of the RAC working group's efforts regarding the scope and applicability of the *NIH Guidelines*, and an overview and discussion of the proposed changes to the requirements for reporting serious adverse events.

Dr. Patterson reviewed the NIH conflict-of-interest rules as a reminder to the RAC members of the importance of impartiality in the conduct of RAC meetings.

II. Minutes of the September 25-26, 2000 Meeting/Dr. Aguilar-Cordova and Ms. Levi-Pearl

Committee Motion

As moved by Dr. Gordon and seconded by Dr. Ando, the RAC unanimously approved the September 25-26, 2000 minutes by a vote of 9 in favor, 0 opposed, and 0 abstained.

III. Review of "Timing Action": Recent Amendments to the *NIH Guidelines* Regarding Research Participant Enrollment and the Process of Protocol Submission and Review/Dr. Patterson

Dr. Patterson described recent changes to the *NIH Guidelines* designed to optimize the RAC review process for clinical protocols in gene transfer research. The *NIH Guidelines* are a set of principles that evolved over the past 25 years for the safe and ethical conduct of both basic and clinical recombinant DNA research. The *NIH Guidelines* delineate the specific roles and responsibilities of the institution at which the research is conducted, the principal investigator, and the local Institutional Biosafety Committee (IBC). Prior to the change published in the Federal Register on Sept. 30, 2000, protocols required Institutional Review Board (IRB) and IBC approval before the RAC review process could be initiated. It was possible that a protocol could be approved by the FDA and patients already enrolled before RAC review occurred. The recent changes included:

- Institutional Biosafety Committee (IBC) approval may not be given until RAC review is completed.
- In depth review and public discussion of selected protocols by the RAC must occur prior to IBC approval.
- Institutional Review Board review and approval may occur before or after RAC review.
- No research participant may be enrolled prior to completion of the RAC review process.

In addition, no later than 20 working days after enrollment of the first study participant, the principal investigator (PI) must submit to OBA a response to RAC recommendations and copies of the final protocol and the IRB and IBC approvals.

These changes are intended to assure local IRBs, IBCs and investigators are apprised of the outcome of public RAC review and discussion. Local review bodies, which generally see only that subset of trials conducted at their institutions, benefit from the collective expertise, broad perspective, and experience of the RAC and from public discussion of scientific and ethical issues. These changes will ensure that no research participant is enrolled until the RAC review process is completed, IBC and IRB approvals are obtained, and applicable regulatory authorizations are secured.

Dr. Patterson indicated that OBA is seeking feedback on the effects of the changes and will be developing a program of outreach to IRBs and IBCs, working closely with the Office for Human Research Protections (OHRP) and FDA. Updates on these efforts will be provided at future RAC meetings.

RAC Discussion

Dr. Mickelson indicated that these amendments do not preclude local committees from setting their own standards for what must be contained within a protocol. Many local committees confer "provisional approval," meaning approval that is not final but that the protocol is ready to be forwarded to the RAC for review.

Dr. Gordon pointed out that PIs have the option of either adopting a RAC recommendation or modifying it as suitable for their protocols. Dr. Patterson clarified that the RAC does not approve protocols but discusses them and issues recommendations. The RAC asks the sponsor or the PI to provide feedback to the RAC on whether and how those recommendations were employed.

Dr. Noguchi reiterated the support of FDA for these amendments.

In response to a question from Dr. Stephen J. Russell, Mayo Clinic, about the consequences of noncompliance with these amendments, Dr. Patterson explained that compliance with the *NIH*

Guidelines is a term and condition of the receipt of NIH funds for recombinant DNA research at an investigator's institution; withdrawal, suspension or termination of NIH funds is therefore a potential consequence of noncompliance. In addition, the NIH will soon publish information about how the sanctions apply specifically to recombinant DNA and human gene transfer research.

Dr. Patterson also spoke to the issue of whether these changes might affect the maturity of protocols submitted to the RAC. Thus far, the changes do not seem to be affecting the completeness of submitted protocols. The 20 protocols received thus far under the amended guidelines have been mature proposals. In addition, OBA has been receiving information-seeking calls from sponsors and PIs early in the process.

In response to a query from Dr. Jeffrey M. Cohen, OHRP, about whether the RAC would be aware of the status of the IRB review of any particular protocol, Dr. Patterson indicated that the RAC may not know how far along in the approval process each protocol has progressed. Dr. Mickelson suggested that the RAC could ask the PI or sponsor to clarify the status as part of the submission cover letter or, if that information is not in the written material, the RAC could ask directly during the RAC meeting. Dr. Gordon stated that RAC review of a protocol should not be influenced by what has been done or not done by the relevant IRB.

Dr. Markert noted that IRBs are receptive to additional information from the RAC, and the RAC's current influence with IRBs appears to be adequate. IRBs do take RAC comments into consideration, so there appears to be no need to formalize this relationship.

Dr. Mickelson stated that additional feedback about the timing action can be sent to OBA by mail, e-mail or telephone.

Public Comment

Dr. W. French Anderson, University of Southern California (USC), commented about the timing of local review committee approval of protocols in relation to RAC discussion. He offered historical background on the reason why the RAC initially required IBC and IRB approval prior to RAC submission, which was to screen out the submission of frivolous protocols that would have to be made public once they were submitted to the RAC. Dr. Anderson agreed that IRB and IBC approval after RAC discussion of the protocol is preferable.

IV. Review of Replication-Competent Retrovirus (RCR) Guidelines/Carolyn A. Wilson, Ph.D., Center for Biologics Evaluation and Research (CBER), FDA

Dr. Wilson presented a summary of the FDA guidance on testing for replication competent retrovirus. Retroviral vectors have been the most commonly used vector in clinical gene transfer research, in part because of their ability to stably integrate into the host DNA, resulting in long-term transgene expression in the host cell. In addition, the vectors do not encode retroviral proteins, thereby avoiding the potential safety concerns that could be caused by an immune response to viral proteins.

Disadvantages of using retroviral vectors include the possibility that vector insertion into a particular locus can cause activation of an oncogenic event and that recombination during vector production could generate replication competent retroviruses (RCR). In order to provide the viral functions, the packaging cells contain viral genetic sequence that could homologously recombine with vector sequence to generate a replicating retrovirus. The risk associated with RCR was demonstrated in a study in which 3 of 10 immunosuppressed monkeys exposed to bone marrow cells transduced with a preparation of RCR-contaminated retroviral vector developed lymphomas and died within 200 days.

Dr. Wilson provided an introduction to the terminology used by the FDA. Packaging cell lines contain the coding sequences for all retroviral structural proteins and enzymes. A plasmid that encodes the vector genome with the inserted transgene is introduced into the packaging cell line. Once the

packaging cell generates vector, it is called a producer cell. A producer cell cloned with high titer and transgene expression is expanded to form a master cell bank. This bank of cells is cryopreserved in sufficient numbers to conduct a clinical trial.

The master cell bank is subjected to a number of safety tests and additional characterizations. In many instances, investigators expand one or several vials from the master cell bank into a working cell bank, then expand the working cell bank to manufacture the retroviral vector. At the end of that manufacturing process, the cells that are left over are called end-of-production cells, and the supernatant containing the vector harvested from those cells is called the production lot. The production lot is the final product if it is injected directly *in vivo* as in some clinical protocols. More commonly, the production lot vector supernatant is cultured *ex vivo* with human cells and these *ex vivo* transduced cells become the final product.

The recommendations for RCR testing put forward in 1993 included testing during many of the stages of vector production. The rationale for testing throughout the production process was based on the fact that recombinant events are random and can occur at any time during the process. The amount to be tested was recommended as 5 percent of the vector containing supernatant and the smaller of 1 percent or $1x10^8$ cells at other stages.

In regard to patient followup, sponsors received a letter from FDA stating that patients who were treated with products that used retroviral vectors as part of manufacture should be monitored for evidence of RCR infection. The recommended time course was once a month during treatment, monthly for the first 3 months after treatment, every 3 months for the remainder of the first year after treatment, and annually thereafter. The FDA also recommended that three different assays be applied to each sample—serologic assays looking for antibody to RCR, reverse transcriptase assays (an enzyme unique to retroviruses), and specific DNA polymerase chain reaction (PCR) assays for RCR sequences in peripheral blood lymphocytes (PBLs).

Beginning at a 1996 forum for gene therapy, the FDA began discussing ways to improve these recommendations. This discussion culminated in the 1999 issuance of a draft guidance document titled "Supplemental Guidance on Testing for Replication Competent Retrovirus and Retroviral Vectors Based Gene Therapy Products During Follow-up of Patients in Clinical Trials Using Retroviral Vectors": in October 2000, a "Final Guidance" document was issued. The Final Guidance states that both cells and supernatant should be tested and describes when the product should be tested for RCR and the amount to be tested (5 percent for small production lots and an algorithmic formula based on the Poisson distribution for large production lots). One change was that only cells in culture for longer than 4 days after exposure to vector *ex vivo* needed to be tested for RCR. Patient monitoring has been modified to sampling at 3, 6, and 12 months after treatment plus archiving of yearly samples (assuming the first three samples are negative). Sponsors also must request assent to autopsy on patient death. Assays can be by either serologic methods looking for RCR-specific antibodies or DNA PCR looking for RCR-specific sequences. Negative results from testing and patient monitoring can be submitted in the annual IND report, and positive results should be reported as adverse experiences in IND safety reports.

The CBER encourages investigators to continue to publish data regarding RCR testing results and to provide permission to FDA to discuss these results publicly. Developing a cumulative database on RCR testing results and methods will enhance FDA's ability to provide further guidance on these topics.

RAC Discussion

Dr. Patterson asked about the extent of sponsor compliance with RCR testing and patient monitoring and followup. Dr. Wilson responded that a partial survey of sponsors in fall 2000 found that compliance with patient followup testing is limited, but these guidelines are relatively new and the data from the survey reflected compliance levels with the earlier guidance. Dr. Noguchi added that compliance in terms of preclinical and routine product characterization is 100 percent, since clinical trials cannot go forward without adequate demonstration of lack of RCR contamination.

Dr. Breakefield questioned whether monitoring only for antibodies to the virion proteins is sufficient. Dr. Wilson responded that clinical trials involving repeat injections should use DNA PCR in PBLs as the assay method of choice so that the result will not be an antibody response to vector that is not still present.

Dr. Markert expressed concern about the logistics of storing these vast numbers of yearly blood samples and who would be responsible for maintaining those samples. Dr. Noguchi summarized the discussion of these issues at an FDA advisory committee meeting. The consensus was to have active monitoring for at least the first 1 to 5 years; beyond that time, there was a clear recognition that archiving additional samples would not be feasible. Additional guidance about archiving samples will be provided by the FDA within the next year, most likely at a meeting in April 2001.

Dr. Greenblatt asked whether the IND would be kept open for continued patient monitoring. Dr. Noguchi responded that FDA's current thinking is to inactivate (not withdraw) the IND, and patient followup data should be submitted yearly as an annual report.

Dr. Mickelson expressed concern about why investigators have not been submitting complete data sets; Dr. Wilson responded that the primary concern expressed by investigators was the expense of doing that much testing. Some sponsors were doing no testing of patient samples or testing only once or twice a year. In changing the recommendations for testing, FDA was trying to find a balance that would result in more participation by sponsors and investigators, thus enhancing the safety database. Dr. Noguchi added that FDA has limited regulatory options, especially when a trial is no longer accruing patients.

Dr. Russell asked how much testing is necessary for the field to be convinced of the safety of retroviral vectors. Dr. Noguchi responded that it is premature for FDA to make predictions on how much and what kind of data would be needed such that patient testing would no longer be necessary.

Dr. Gordon discussed the issue of patient compliance with long-term follow-up where blood samples are required. Although long-term follow-up is intended to safeguard patients and characterize the administered agent, he expressed concern that patients would see providing these samples as a significant imposition and having no benefit to themselves or others from simply archiving samples.

Dr. Patterson pointed out that NIH is planning a conference on long-term follow-up, of which testing for RCR will be one component. The conference will examine the practical strategies for obtaining and storing data over the long term.

Public Comments

No public comments were offered.

V. Retroviral Vector Targeting/Stephen J. Russell, M.D., Ph.D., Mayo Clinic

The goal of research on targeting retroviral vectors is to develop a vector that, when injected into a patient's vascular system, will selectively transduce the target disease sites and be selectively expressed at those sites to bring about a therapeutic effect. Delivery targeting involves selective accumulation of the vector at the sites of disease and gene transfer into the target cells. Expression targeting is achieved through the use of regulatory elements that limit gene expression to the target cells. A third method is to target the effect of the gene product to exclusively have a therapeutic effect on the target tissue.

The goals of targeted delivery are specific accumulation of the vector at the disease sites and, once there, selective transduction of the target cells. For retroviruses such as murine leukemia virus (MLV), the envelope glycoprotein on the virus surface mediates binding to target cells and subsequent fusion and entry. Vector targeting requires modifying the envelope either in the preformed virus or through a genetic approach. Modifications to preformed viruses include coating the virus with a chemical

modification or using a bifunctional crosslinker that binds both the virus and the receptor. In terms of genetic modifications, the envelope can be engineered to change binding specificity or the envelope can be entirely replaced by envelopes from other viruses, an approach called pseudotyping. MLV can be pseudotyped with a variety of different glycoproteins, but most of these have a broad binding specificity.

Regions within the envelope domains have been identified which will tolerate insertion or substitution of different targeting domains from growth factors, antibody fragments, adhesive proteins, oligomerization motifs or protease cleavage signals. One targeting strategy is host range extension in which the tropism of an ecotropic virus that binds only mouse cells is extended to allow binding to human cells. The opposite approach, host range restriction, involves changing an amphotropic virus that binds many human cells to bind only specific cell types. This can be accomplished through inverse targeting, for example, when the vector is modified to display epidermal growth factor (EGF). The virus then binds cells with the EGF receptor but is unable to enter and infect them. Only cells without the EGF receptor can be infected through the wild type viral receptor. In the protease targeting strategy, a domain that blocks infectivity is introduced into the envelope along with a protease cleavage signal. In the presence of cellular proteases, the blocking domain is cleaved allowing the virus to infect the cell through its natural entry pathway. Retargeted viruses are inefficient frequently because, while virus attachment does not appear to be receptor driven, virus entry is and there are few receptors that can efficiently mediate entry.

Infectivity is less of an issue if the vector can be modified to accumulate at the desired site. This approach was taken by Drs. Anderson, Hall and Gordon, University of Southern California. The von Willebrand factor collagen binding peptide was inserted into the N-terminus of the amphotropic envelope. This modification did not change viral entry by the ampho receptor but rather caused accumulation of vector at sites of exposed collagen in tumor blood vessels. This type of *in vivo* vascular delivery raises many issues, including the nature of the microvasculature the vector will pass through, the potential for interaction with plasma proteins, the regional density of receptors, and the solubility of the vector. There is limited biodistribution information for intravenously injected retroviral vectors. Lentiviral vectors may be more suitable for this type of study because they transduce non-dividing cells unlike retroviral vectors that transduce only dividing cells. Injection of luciferase lentiviral vectors has shown highest luciferase expression in the liver, spleen and heart while genome detection was highest in the liver, spleen and muscle.

The use of targeted vectors raises some new safety concerns. A cell growth or signalling peptide displayed on the virus may stimulate a biological response in the target tissue. Even if the peptide displayed is human in origin, in the new context it may stimulate a potent immune response. Safety issues would be greater with host range extension than restriction strategies.

RAC Discussion

Dr. Noguchi asked to what extent the biodistribution data were due to the nonspecific binding of viruses rather than specific increased receptor binding. Dr. Russell responded that, because the *in vivo* and tissue culture situations are completely different, it was difficult to comment.

Dr. Gordon requested that Dr. Russell elaborate on the discrepancy between the amount of genomic DNA detected in myocardial cells and the level of expression and address whether the cardiac myocyte is more conducive to expressing virally encoded genes. Dr. Russell explained that this type of study has limitations; the promoter driving expression of the luciferase transgene is the cytomegalovirus (CMV) promoter. Comprehensive information is not available about which tissue types will give the highest level of expression with the CMV promoter.

Public Comments

No public comments were offered.

VI. Discussion of Human Gene Transfer Protocol #0010-417: *Tumor Site-Specific Phase I/II Evaluation of the Safety and Efficacy of Hepatic Arterial Infusion of a Matrix-Targeted Retroviral Vector Bearing a Dominant Negative Cyclin G1 (dnG1) Construct as Treatment for Colorectal Carcinoma Metastatic to Liver*

Principal Investigator:	Heinz-Josef Lenz, M.D., USC
Other Investigators:	Frederick L. Hall, M.D., USC
Sponsor:	Erlinda M. Gordon, M.D., Gene Therapy Labs/USC
RAC Reviewers:	Drs. Ando and Breakefield and Ms. King
Ad Hoc Reviewer:	Stephen J. Russell, M.D., Ph.D., Mayo Clinic

Protocol Summary

Colon cancer is a leading cause of cancer deaths in the United States and in Europe. For most patients, the cancerous growth can be removed by surgery, but some individuals experience a recurrence of the cancer despite surgery, radiation treatment and chemotherapy. In such patients, the cancer is likely to spread to the liver, and fewer than 5 percent will survive beyond 16 months despite aggressive chemotherapy. A common site of metastasis of colon cancer is the liver.

The investigators have developed a matrix (collagen)-targeted retroviral vector bearing a dominant negative cyclin G1 construct (Mx-dnG1). The von Willebrand factor collagen binding peptide was inserted into the N-terminus of the amphotropic envelope. This targeted vector accumulates at sites of exposed collagen caused by tumor invasion or tumor vessel formation, thus promoting tumor site-specific gene delivery. Cyclin G1 is a cell-cycle element that is overexpressed in a subset of cancer cells. The approach utilizes a dominant negative G1 cyclin to inhibit the function of G1 cyclin in cell cycle and tumor cell growth. In a nude mouse model of liver metastasis, a significant reduction in size of the tumor foci in the liver was observed in Mx-dnG1 treated mice compared to those of control vector- or PBS-treated animals.

The goal of the clinical trial is to evaluate the safety of the Mx-dnG1 vector in patients with colon cancer that has spread to the liver. The Mx-dnG1 vector will be injected into the liver artery through a pump for 6 hours daily for 5 days. The dose of the vector will be increased according to protocol specifications.

Basis for Pubic Review

Eight RAC members recommended that the protocol warranted public discussion for the following reasons: the protocol represents the first use of a hepatic arterial injection of a targeted retroviral vector, and unresolved issues relating to the appropriateness and adequacy of non-human primate evaluations. The following RAC members, Dr. Ando, Dr. Breakefield and Ms. King, were assigned to review the protocol in depth. Dr. Russell served as *ad hoc* reviewer. The investigators responded to their previous comments in writing and during this meeting.

RAC Discussion

Dr. Breakefield stated that this is a very interesting protocol that takes on a very serious disease. She grouped the novel aspects into three categories: liver toxicity, the nature of the therapeutic gene product, and the potential for generating RCR because of the way the vector will be produced. Since intra-arterial delivery to the liver of large volumes of vector is novel and not testable in mice, testing in a large animal model would be useful especially for biodistribution studies. She was also interested in the potential effects of dnG1 in normal dividing cells, such as in the spleen, to decrease proliferation.

Dr. Ando discussed safety concerns regarding how SV40 T-antigen contamination will be adequately characterized and estimated and how to ensure purification of the relatively large volume that will be injected directly into the hepatic artery. He suggested that the investigators test the stability of the retroviral preparation using the clinical infusion setup. Patients should practice barrier contraception since animal studies revealed positive vector biodistribution to testes. He also suggested that it would

be important for the staff doing the injections to be trained by people who have specific experience in hepatic artery infusion of adenovirus.

Dr. Russell stated that this is a very elegant targeting strategy and will be the first use of a retrovirus targeted in this way. He expressed concern about the product complexity; although the preclinical toxicology studies are reassuring, they were conducted in mice using a delivery route different from that proposed for the clinical protocol. Given the potential liver toxicity, Dr. Russell suggested that the investigators consider enrolling only those patients who have normal liver function, although this may be problematic because almost all patients with metastatic cancer in their liver will have at least slightly abnormal liver function. Dr. Russell also raised questions about whether the inserted bovine peptide had been shown to bind to human collagen and whether the investigators can provide data to show that cyclin G1 is overexpressed in primary human colon cancer cells. He also asked about the appropriateness of a statement in the informed consent document indicating that research participants will be charged for some of their care given that the goal of the study is to assess the toxicity of a new therapeutic agent.

Ms. King limited her comments to issues surrounding the consent document process. She requested a clearer explanation of some aspects of the study, including a description of the risks and the meaning of a dose-escalation and urged that the potential benefits of this very early trial not be overstated in the consent form. A request for autopsy should be included. She suggested that the term “gene therapy” be changed to “gene transfer” and that the term “treatment” be changed to “infusion” or “intervention.” The risks of hepatic arterial infusion should be described in the risks section of the consent form. Ms. King also suggested replacing the boilerplate statement about the potential for direct benefit to research participants with a more meaningful statement, and she offered sample language for the investigator’s consideration.

Dr. Markert raised a question about the protocol’s lack of a Data and Safety Monitoring Board (DSMB) or a Good Clinical Practices auditor.

Investigator Response

Dr. E. Gordon responded to RAC members’ oral comments. Regarding concerns about the large volume of vector administered via hepatic artery infusion, she stated that, in research participants with metastatic cancer, researchers must consider the risk-benefit ratio of an agent that has been demonstrated *in vitro* as well as in small-animal studies. Large-animal studies are not usually required when this extent of efficacy has been demonstrated. She agreed that the researchers should perform biodistribution studies of peripheral blood lymphocytes.

In response to Dr. Breakefield’s concern about the possible effects on splenic function, Dr. E. Gordon agreed that there is no direct way to evaluate splenic function, except to measure immunoglobulin levels. Dr. Lenz concurred, stating that because of the lack of good markers, it is difficult to evaluate splenic toxicities in patients with hepatocytic disease.

Dr. Lenz then responded to other RAC members’ comments. Regarding volume, he stated that the recommended highest rate of intra-arterial hepatic infusion is about 300 ml per hour whereas the proposed infusion rate will be 150 ml per hour. Regarding liver function and patient inclusion criteria, Dr. Lenz explained that elevated transaminases do not necessarily signify liver dysfunction but only that tumor in the liver is affecting the liver transaminases. Infusion using the hepatic artery is an accepted mechanism to treat patients with liver disease; this method provides the vector to the tumor in the most efficient way and has been proven not to be more toxic than the portal vein route. He agreed to make the requested changes to the informed consent document.

Drs. Russell and Breakefield brought up the possibility of conducting large-animal studies using a dog or pig before testing this vector in humans. Dr. Anderson responded that while it would theoretically be more comforting to have conducted studies using a large-animal model, researchers have infused large animals with retrovirus (although not this specific retrovirus) without difficulty. Dr. Gordon added that a

larger animal would not be a relevant model unless it had a liver tumor. Dr. Anderson pointed out that even 10 years of experience with intrahepatic infusion into nonhuman primates would not make any difference in what is seen in the first human patient; Dr. Russell acknowledged this point.

In response to Dr. Breakefield's and Dr. Markert's concerns about determining the RCR assay's sensitivity, Dr. Gordon and Dr. Anderson stated that the researchers will ensure that the testing laboratory meets all FDA criteria.

Dr. Markert reiterated her concern that the protocol did not include a monitoring board for quality control. Dr. Gordon stated that, as investigators in a comprehensive cancer center funded by the National Cancer Institute (NCI), the researchers have in place a patient monitoring system, an internal review committee, and committees on internal and external audits and controls. Dr. Markert clarified that she was suggesting that this protocol have its own DSMB.

Public Comments

No public comments were offered.

RAC Recommendations

Dr. Mickelson summarized the following RAC recommendations:

- Since this is the first use of transient transfection of 293T cells to generate retroviral vectors for clinical application, characterization of the vector product should include determination of levels of trace contaminants such as SV40 T antigen DNA and protein, cellular DNA and debris, bovine serum, and characterization of the physiocochemical properties of the vector to detect aggregation that may affect its biodistribution. The assay for detection of RCR should be defined as to the level of sensitivity. Passage of vector stocks on human cells would allow amplification of RCR as it is present and assaying on human cells as well as Mus dunni cells would allow maximal sensitivity.

- A large animal model (e.g., porcine or canine) should be employed for the analysis of any acute toxicities that may be associated with hepatic arterial administration of large volumes of the vector-containing supernatant that will be used in the clinical protocol.

- In regard to oversight, the establishment of a separate data safety monitoring board would ensure that the trial received appropriate attention.

- To improve its comprehensibility, the informed consent document should be reorganized. In addition, potentially misleading terms such as "gene therapy" and "treatment" should be replaced with more neutral terms such as "gene transfer" and "infusion" or "intervention." A reference to a request for autopsy should also be included. Testing of sperm for retrovirus integration is an FDA requirement for retroviral vector protocols and should be included in the protocol and informed consent document.

Committee Motion

It was moved by Dr. Breakefield and seconded by Dr. Ando that the four recommendations expressed the concerns of the RAC. The vote was 9 in favor, 0 opposed, and 2 abstained.

VII. Discussion of Human Gene Transfer Protocol #0010-423: *Laminin 5 β3 Gene Therapy for Junctional Epidermolysis Bullosa*

Principal Investigator: Alexa Boer Kimball, M.D., Stanford University
Other Investigator: Alfred T. Lane, M.D., Stanford University

Sponsor:	N/A
RAC Reviewers:	Drs. Macklin, Markert, and Mickelson
Ad Hoc Reviewer:	None

Protocol Summary

Junctional epidermolysis bullosa (JEB) is one of several inherited blistering skin diseases. Children with JEB are born lacking a protein called laminin 5 β3. Without this important protein, which helps to adhere the epidermis to the dermis, the epidermis is easily rubbed off in blisters. Even holding these children can cause sores and injuries. Ninety percent of affected children die within the first year of life, usually from severe infections or lung problems. The current treatment for this kind of JEB consists of management of the blisters. There are currently no therapies available to alter the course or severity of the disease.

JEB patient keratinocytes were grown in culture, transduced with a retroviral vector capable of sustained cutaneous expression of laminin 5 β3, and grafted on immune-deficient mice. The same approach will be used to generate corrected autologous keratinoctye sheets and graft them onto blistered, ulcerated areas of diseased skin of JEB research participants. Two transduced skin grafts will be evaluated for attachment to affected skin and expression of laminin 5 β3. The graft sites will be compared to two ungrafted sites which will be treated with conventional wound care. The patients will be followed at least twice a year after the first 6 months.

Basis for Public Review

Six RAC members recommended that this protocol warranted public discussion for the following reasons: the involvement of a new disease, vector construct, functional gene, and very young research participant population and questions about potential benefit. Dr. Macklin, Dr. Markert, and Dr. Mickelson were assigned to review the protocol in depth and submitted written comments, to which the investigators responded in writing and during this meeting.

RAC Discussion

Ms. King commented that the investigators have been presenting this trial as a treatment program rather than as Phase I research, and should not present it as such to the IRB and the parents of research participants. Ms. King also did not view this research as a minor increase over minimal risk, and thus questioned the prospects for direct benefit. She requested more information on graft failure in humans and on how researchers would distinguish the source of sepsis as related to treatment or disease course.

Dr. Markert noted that her written comments had been addressed satisfactorily. She suggested that the 10 research participants be enrolled more slowly so that the risk of immune problems could be assessed for each one. She also questioned how the investigators will distinguish between infection caused by the recombinant graft and infections caused by the underlying disease (90% of patients die from infections in their first year). Given how fragile the research participants are, the informed consent document needs to be clearer on the risks associated with any procedure done on the child, the risk of death, and request for an autopsy.

Dr. Mickelson's comments centered on six issues: the risks to such young children may be outweighed by any possible benefit; in regard to potential immune response problems, older patients or individuals who carry missense mutations as opposed to deletions might be more appropriate initial research participants; given that a large percentage of patients die from pulmonary failure, the actual benefits to participants with successful grafts should be discussed; whether the disease selection was being driven by the limitations of the skin grafting technology to be most useful only for treatment of diseases in which there is a complete lack of laminin 5; possible heterogeneity of the cell types generated by the Epicel technology; and how well the grafts were characterized.

Since Dr. Macklin had not yet arrived, Ms. King presented Dr. Macklin's comments which were focused on the ethical aspects of the protocol. She raised questions about whether studies of this type should be conducted only on adolescents or young adults capable of providing consent; and whether the risks to participants are too great to warrant conducting the study even if eventual benefits accrue to others. Consent document issues noted by Dr. Macklin included the use of terms and wording that might imply treatment rather than experimentation and the statement about the financial responsibility of families for hospital and physician expenses, wound dressing, and medications.

Dr. Ando pointed out the following issues: a clear description of the packaging cell line is needed; the complexity of the manufacturing process; and that RCR testing in humans as proposed does not follow current recommended FDA guidelines. He also raised questions about the general and individual gene polymorphisms and how they might correlate with immunogenecity.

Dr. Friedmann asked for clarification about the target tissue and the possibility of topical delivery of vector. Dr. Lane explained the target is keratinocytes of the epidermis and topical delivery would not be possible because the target is not accessible in intact skin or present after blistering.

Dr. Juengst questioned the researchers' ultimate clinical vision—whether or not the investigators envisioned eventually grafting a subject's entire skin.

Dr. Cohen reiterated Ms. King's comments about the determination of level of risk and the prospect of direct benefit in this study, and asked which category of research with children was approved by the IRB. He also asked whether skin grafts in general are a treatment for this disease.

Dr. Chow observed that the only risk would be immunological rejection which could be treated by removing the graft. She suggested that the children would not be much worse off than before the procedure. She would not classify the study as high risk to the participants.

Dr. Gordon pointed out that molecular diagnosis could be provided to families to use for future reproductive decision making.

Ms. Levi-Pearl reemphasized Ms. King's comment about the enormous vulnerability of this patient population.

Investigator Response

Dr. Lane began the investigators' responses by addressing the issue of subject age. Worldwide there are 100 to 200 children alive with JEB who are older than 1 year, but it is unknown how many of those have the mutation in laminin 5 β3 as opposed to other genes involved in the disease. Though the researchers were willing to try to recruit some of those individuals to participate in the clinical trial, Dr. Lane expressed concern that these individuals would have mostly facial wounds and that grafting near the eyes is problematic. In regard to trial risks, Dr. Lane explained that the study procedures should not be more traumatic than the initial diagnostic procedures and that the process of changing the wound dressings on a regular basis and manipulating these children through gauze is familiar to these families and to their medical caretakers. Skin grafts have been used to treat other EB diseases but JEB cells are too difficult to grow *in vitro* to transplant. The persistence of the transduced grafts on the SCID mice for 2 months suggested that stem cells had been successfully transduced which should allow for long term expression in humans.

Dr. Patterson asked the investigators to comment on one of the issues under discussion with the FDA—whether the Epicel (Genzyme) technology was being classified as a xenotransplantation procedure since it involves the use of an irradiated murine feeder layer. Dr. Wilson clarified that Epicel has been determined to be a xenotransplantation product; and as such, the FDA has advised Genzyme that specific issues in the informed consent document and patient monitoring need to reflect current policy requirements in this area. Dr. Patterson suggested that the researchers look at the Public Health Service Guidelines on infectious disease issues in xenotransplantation, which outline the strategies for following patients and the types of tests that should be done.

Dr. Kimball responded to Dr. Markert's concern about the frequency of participant recruitment by stating that the researchers anticipate it will take years if ever to recruit all intended research participants. Regarding management of immune reactions to the laminin 5, Dr. Kimball explained that acquisition of antibodies could be managed with topical steroids.

In response to Dr. Mickelson's question about whether the investigators expect to lengthen the lifespan of these children, Dr. Kimball responded that small skin grafts probably would not extend life but more extensive grafts might make an impact. In the short run, the researchers hope to reduce suffering by grafting some small areas, thus producing some real potential benefit.

Dr. Chow cautioned against optimism because most of the cells transduced will be trans-amplifying cells and not stem cells. Dr. Kimball acknowledged that fact.

Dr. Lane addressed the perception that they may be approaching this technology as if success was guaranteed. He said that, in addition to giving hope to the families the researchers are trying to find an approach that will be successful. The researchers have tried to do all the safety monitoring possible and have tried to inform the patients as accurately as they can. The next step is to move forward with the study to find out how these children respond.

Dr. Friedmann asked about the possible use of a gene gun. Dr. Lane explained that the gene gun was considered, but the technology has not been able to transduce stem cells as has been achieved in the mouse model using skin grafts in which expression persists for longer than 2 months.

Dr. Juengst asked the researchers whether these patients will need skin grafts for as long as they have any of their original skin. Dr. Lane responded that there will be major sites of trauma that will need to be grafted—hands, buttocks, trunk, and face.

Drs. Kimball and Lane pointed out that the researchers are arranging for one of the members of the oversight committee (a bioethicist) to be present during the consent process as an advocate for the patients.

Public Comments

No public comments were offered.

RAC Recommendations

Dr. Mickelson summarized the following recommendations offered by RAC members:

- Because the graft technology used by Genzyme to grow the transduced keratinocytes requires irradiated murine feeder cells, xenotransplantation issues including possible follow-up studies should be raised in the informed consent document. Different versions of the informed consent document will be needed to increase comprehensibility to both adult (parents' consent) and child participants (child's assent).

- Information gained concerning polymorphisms identified during the study will be useful for genotype/phenotype correlation and for assessing intervention response. If a research participant makes a laminin 5 β3 protein, it is less likely that antibodies or T-cell responses will be formed against the product. The research participants making no protein are more likely to have immune based problems.

- The use of a third-party patient advocate was noted to be particularly useful given the vulnerability of the research participants.

! The RAC requests status reports after treatment of the first patient. Of particular interest would be information on the generation of humoral or cellular immune responses and whether adverse events were due to the underlying disease or the treatment.

Committee Motion

As moved by Dr. Juengst and seconded by Dr. Gordon, the RAC voted unanimously in favor of these recommendations. The vote was 11 in favor, 0 opposed, and 0 abstained.

VIII. Data Management/Dr. Greenblatt

Dr. Greenblatt reported that a total of 420 gene transfer research (GTR) protocols have been submitted to OBA since the beginning of the field in 1989. Since the past reporting period, 18 new protocols were submitted; 12 were exempted from review; and 6 are being publicly reviewed at this RAC meeting.

Of the 420 protocols, 381 are for GTR, 37 involved cell marking, and 2 were conducted with normal volunteers. Breakdown by disease indication of the 381 GTR protocols indicates that:

- 258 were for cancer;
- 49 were for monogenic diseases (cystic fibrosis was the most frequent);
- 34 were for infectious diseases (all but 1 for human immunodeficiency virus [HIV]);
- 40 were for other diseases (coronary artery disease [15] and peripheral artery disease [14] were the most frequent).

Amendments and Updates and Serious Adverse Events

Since September 1, 2000, 50 amendments and updates have been submitted to OBA, almost all of which involved notifications about new investigators, new clinical sites, protocol closings, changes in informed consent or eligibility, minor protocol modifications, and/or modifications made as a result of FDA review.

Analysis of serious adverse event (SAE) reporting for the period September 1 to December 1, 2000 indicated that 75 percent were initial reports and 25 percent were followup reports. Most were considered not associated with gene transfer. Eleven percent of the SAE reports were possibly associated and unexpected. Dr. Greenblatt briefly discussed one amendment to Protocol #9902-284 (Factor VIII for severe hemophilia A)—in which a retroviral vector was injected intravenously. Vector sequence was detected in one semen sample of one participant in the trial. Subsequent samples from the participant were negative. Drs. Greenblatt and Gordon deferred further discussion until after the following two presentations (see next two sections).

Dr. Greenblatt briefly described several events from clinical trials involving angiogenic growth factors in which tumors developed in patients. Genes for growth factors such as fibroblast growth factor (FGF) or vascular endothelial growth factor (VEGF) have been administered in gene transfer studies to research participants with coronary artery disease and peripheral vascular disease in the hope of stimulating new blood vessel formation to replace the blood vessels that are occluded or blocked. Tumors, like organs, need blood vessels to grow; therefore, angiogenesis is required for a tumor to grow beyond small size. One potential problem with the use of vectors encoding genes for angiogenic factors is the theoretical possibility that such vectors may locate within the tumor or within endothelial cell precursors so that angiogenic factors would be produced, resulting in new blood vessel formation within tumors and the potential for tumor growth.

Dr. Greenblatt posed several questions to the RAC regarding the information contained in these reports: should there be exclusions for patients with tumors and for those at high risk for cancer; should mention

of the theoretical risk of tumor promotion be included in the consent document; and, if tumors arise in patients subsequent to administration of vectors encoding genes for angiogenic factors, should the tumors should be tested for the presence of vector sequences. Dr. Stephanie L. Simek, CBER, responded that all gene transfer trials within the FDA's purview exclude research participants who have neoplastic disease with the exception of resected basal cell carcinoma. Testing the tumors for vector sequence would not be informative unless integrating vectors were used. Despite the lack of information gained by a negative result, several RAC members advocated for the evaluation of tumor tissue for vector sequence. These issues were to be further explored the next day at the Third Gene Transfer Clinical Research Safety Symposium: Safety Considerations in Cardiovascular Gene Transfer Clinical Research.

IX. Biodistribution of Gene Therapy Vectors for Phase I Clinical Trials/Ann M. Pilaro, Ph.D., CBER, FDA

Dr. Pilaro provided a summary of the FDA policy regarding biodistribution studies, and their importance in determining risks for clinical trials. As an introduction to the following presentation on the detection of germ line transduction in a retroviral vector trial, she described the expected studies for gene transfer vectors and gonadal dissemination. Biodistribution is defined as absorption, distribution, metabolism, and excretion (ADME) of a drug or biologic. Exposure data in animals should be evaluated prior to human clinical trials, and ADME data in animals should be available to compare with human data from clinical trials. In gene transfer research, biodistribution studies are designed to address absorption and distribution, particularly dissemination of vector to the germ line and nontarget tissues. Preclinical animal studies are designed to determine the distribution of vector to sites other than the intended therapeutic site using direct DNA polymerase chain reaction (PCR) or TaqMan as the assay.

During the March 1999 RAC meeting, issues associated with gonadal distribution were reviewed, including reproductive physiology, gonadal biodistribution results to date, and potential risks of positive signal to future generations. Three conclusions were made at that meeting: the risk of foreign gene transfer to germ cells and to future progeny were perceived to be low; data on biodistribution to gonads were not necessary prior to all Phase I clinical trials; and the lack of data and unknown risks should be addressed in the consent. Dr. Pilaro offered sample language for relevant informed consent documents.

Biodistribution studies may not be necessary or be postponed when using a previously defined vector, when the transgene product is innocuous if expressed ectopically, and when the size of the plasmid vector is not excessively larger than others used previously. Biodistribution studies are required prior to Phase I trials when using a new class of vector, when there is a change in formulation, when there is a change to an intentional systemic route of administration with a vector established as safe, and when the transgene has the potential to induce toxicity if aberrantly expressed in a nontarget organ. If the data had not been supplied prior to a phase I trial, it must be obtained either from preclinical animal studies, clinical samples or a combination of both.

VIII. Risk of Germ-Line Transduction After Direct Injection of Retroviral Vectors/Deborah Hurst, M.D., Chiron Corporation

Dr. Hurst discussed the history of Chiron's retroviral vectors in the clinic, the rationale for current use of retroviral vector by the intravenous (IV) route for hemophilia A (Factor VIII [FVIII] deficiency), preclinical data on germ-line transduction, and clinical data from an ongoing FVIII trial.

Preclinical biolocalization studies of intravenously administered retroviral vectors were performed in rabbits and dogs. No positive semen samples were found in the studies.

For the clinical trials, it was expected that cells susceptible to transduction would be those both dividing and on the blood side of the sertoli cell barrier (i.e. differentiating spermatogonia and the stem cells). Based on the maturation rate of these precursor cells, transduced sperm would be detectable from 40 to

92 days post vector administration. Semen samples are tested before, during and after this period and any positive result is followed by additional testing until three consecutive samples test negative.

In the phase I multicenter study of FVIII retroviral vector in research participants with severe hemophilia A, human semen PCR results to date are that 61 of 63 semen samples tested from 11 research participants were negative; 1 was positive; and 1 was indeterminate. Possible sources of the positive PCR test result were transduced somatic cells (granulocytes, macrophages, lymphocytes, or epithelial cells) in the semen, test contaminants, and sperm produced from transduced spermatogonia. Results of the human semen PCR analysis are that, at a 99 percent confidence level, the worst-case frequency of a transduced sperm is 1 in 3,100,000 to 8,600,000 cells. No positive samples have been detected after the first cycle of spermatogenesis.

Dr. Hurst concluded that current human semen data are consistent with preclinical data—the probability of a germ-line cell being transduced is very low, and the probability of inadvertent germ-line transmission of this retroviral vector genome at the current dose is remote.

RAC Discussion

Dr. Gordon stated that there is much concern about germ-line insertion and that it is viewed much differently from all other possible side effects of gene transfer. To examine the risks of germ-line insertion and determine how to minimize those risks, he suggested that a systematic review of the susceptibility of male and female gametes would be required. The susceptible target cells in the male are the premeiotic spermatogonia because the blood-testes barrier will block almost all gene transfer reagents from penetrating to the postmeiotic cells. Because semen contains a heterogenous cell population, a positive PCR signal from semen may not indicate transduced sperm. Trials that deal with spermatogenic cells from the other side of the blood-testes barrier (e.g., for prostate gene therapy) pose a more significant risk; PCR positivity in semen will occur. Therefore, he suggested that men who participate in gene transfer trials and who intend to reproduce should bank their sperm and use barrier contraception.

In the female, the most susceptible cell is the primordial follicle. Once a follicle starts developing, the follicle cells begin to lay down a glycoprotein egg shell, called the zona pellucida, which is impenetrable to retroviruses and adenoviruses. Because primordial follicles can be transduced and then held for many years before ovulation, the situation in females is more complicated. Oocyte freezing is not yet efficient enough to be an option. He stated his belief that reproductively competent women should not be excluded from gene transfer studies.

Preimplantation embryos with a breach in the zona pellucida are among the cells most susceptible to DNA transformation. Consequently participants should be advised carefully about not undergoing assisted reproduction procedures during the course of gene transfer.

Dr. Gordon summarized the animal research being conducted in his laboratory: Developing mouse gametes have been exposed to significantly more virus than would ever be encountered in the clinical setting, and results to date indicate no transfer to ovarian follicles, spermatogenic cells, oocytes without their zona pellucidas, or mature eggs. Testing of mouse fetuses is ongoing. These types of studies should increase confidence in the safety of administering gene transfer reagents to people who are reproductively active.

Public Comments

No public comments were offered.

XI. Development of the Genetic Modification Clinical Research Information System: Overview/James D. Foss, M.B.A., Stellar Systems

Mr. Foss described the database development. Phase I is to develop a pilot database that will be put on the Web by the end of the year. Phase II is the final product, the Genetic Modification Clinical Research Information System (GeMCRIS), which is to be ready for first draft release in Spring 2001. The ultimate goals are to enhance the science and safety of gene transfer clinical trials and public awareness of clinical GTR.

In the pilot version, data will be refreshed periodically and a means for capturing public comment will be made available. Mr. Foss demonstrated sample "Web presence" screens, which are accessed through the OBA home page, including searching through the list of clinical trials in human gene transfer, querying the pilot database, and obtaining reports.

The users of the database are expected to be a diverse group including NIH, FDA, patient communities, the general public, policy makers and the media. Input from user groups will be obtained via the Web and consultations. Focus groups will be formed to obtain additional input from external users.

Phase II version will be a long-term system that maintains clinical trial and IBC information, tracks clinical trial reviews, maintains protocol followup information, and interfaces with the "e-records management" system that OBA is currently developing. The system will enhance public awareness of the scope of clinical trials and will generate preformatted reports for Federal and public users. The database will be developed through evolutionary methodology in which a stable system is built quickly but, following user feedback, other functions will be added in subsequent versions.

Controlled vocabularies will be used, including the Medical Dictionary for Regulatory Activities which has been endorsed by the International Conference on Harmonization. Candidate areas for controlled vocabularies include disease (the clinical indication for the trial), SAE terms, vector, DNA insert (transgene), and target.

Mr. Foss emphasized that the initial database available on the Web will be a pilot. Longer term system development will follow in stages, including a system strategy for software releases. The keys to success are the controlled vocabularies to be used for product and clinical terminology and user input about information needs.

RAC Discussion

Dr. Markert requested that the database be usable by RAC members to review protocol comments rather than receiving many e-mails regarding a specific protocol. Dr. Patterson responded that the RAC is one of the principal user groups from which feedback will be requested and that a protocol review strategy is being developed that will use the database as a key tool.

Dr. Ando asked whether there will be an effort to develop templates or to electronically transfer all the reports (serious adverse events, annual reports, etc.). Mr. Foss replied that one of the goals will be to expedite SAE reporting using a Web site separate from the database.

XII. Day One Closing/Dr. Mickelson

Dr. Mickelson thanked the participants and adjourned the first day of the December 2000 RAC meeting at 5:20 p.m. on December 13, 2000.

XIII. Day Two Opening Remarks/Dr. Mickelson

Dr. Mickelson opened the second day of the December 2000 RAC meeting at 8:25 a.m. on December 15, 2000.

XIV. Discussion of Human Gene Transfer Protocol #0009-411: *Restenosis Gene Therapy Trial—Phase I Study (REGENT I)*

Principal Investigator:	Richard E. Kuntz, M.D., M.Sc., Brigham and Women's Hospital, Beth Israel Deaconess Medical Center, and Harvard Medical School
Sponsor:	Heiko B. von der Leyen, Priv.-Doz.Dr.med., Cardion AG, represented by North America LLC
RAC Reviewers:	Drs. Friedmann and J. Gordon and Ms. Levi-Pearl
Ad Hoc Reviewer:	Edith Tzeng, M.D., University of Pittsburgh Medical Center-Presbyterian

Protocol Summary

About 1 million people in the United States are treated with angioplasty using widening devices such as stents each year. The process of angioplasty traumatizes the artery inducing a tissue injury response. In a sizable majority of patients (20-30%), this response results in a renarrowing of the artery called restenosis. Restenosis is an especially common occurrence among patients with diabetes. This trial will target research research participants with diabetes who have stents, long lesions and moderate-to-small vessels with a high rate of restenosis.

This gene transfer protocol employs a DNA plasmid vector encoding the gene for inducible nitric oxide synthase (iNOS) administered in a lipoid fluid. Nitrous oxide (NO) is normally produced in the walls of blood vessels. Injury to the endothelium reduces NO production and induces the local expression of mitogens and chemotactic factors that stimulate vascular smooth muscle and leukocyte migration and proliferation resulting in restenosis. NO inhibits smooth muscle proliferation. Treatment with the gene for iNOS may increase the amount of NO in the wall of the heart artery, thereby decreasing the chances for this artery to renarrow. If the iNOS gene transfer procedure is successful in preventing or diminishing restenosis of the cardiac blood vessels, the requirement for additional treatment of the narrowed, stented artery by either angioplasty or a surgical procedure may be reduced or eliminated.

In animal studies where the iNOS-lipoplex gene product was given directly into the arterial wall before the vessel was experimentally narrowed, less arterial narrowing was seen. In this clinical trial, the iNOS-lipoplex gene product will be applied directly into the inside wall of the narrowed artery using a device called the Infiltrator catheter.

To ensure appropriate monitoring of patient safety, physicians experienced in heart catheterization procedures will evaluate any adverse effects in the study. The judgements of these physicians will then be reviewed by an independent group of doctors who are experts in the conduct of gene therapy clinical trials.

Basis for Public Review

This protocol was determined to warrant public review by three RAC members for the following reasons: the novel delivery scheme and novel use of an iNOS vector for restenosis. Dr. Friedmann, Dr. Gordon and Ms. Levi-Pearl were assigned to review the protocol in depth and submitted written comments, as did *ad hoc* reviewer Dr. Tzeng, to which the investigators responded in writing and during this meeting.

RAC Discussion

Dr. Gordon's comments related to the device's potential for traumatic effects and whether the animal models were representative of human disease since the animals did not have coronary disease. In potential research participants with an underlying pathology, the amount of gene transfer and the level and duration of iNOS expression necessary are not known. Dr. Gordon also expressed concern about

the potential for germ-line transmission of exogenous DNA in both female and male research participants.

Dr. Friedmann's comments focused on the efficiency of transfection, the cell types transfected, and the possible effect of iNOS on those cell types. He questioned whether pharmacology toxicology studies had been conducted in animals with stents. Dr. Friedmann questioned the monitoring procedures and how the clinical end points would be evaluated—when and how extensively the investigators would look for hemangioma and other potential complications. He suggested that clarification was needed regarding who would have access to patient records.

Ms. Levi-Pearl's comments focused on the consent document. Her suggestions for improvement of the consent document included the following: The experimental nature of this study should be repeated throughout the consent form; the introduction should emphasize the importance of the potential participant's decision making (e.g., "Do not sign this form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions."); the complex procedures and devices to be used should be clarified, perhaps via a question-and-answer format; and explanation of medical terms that may not be readily understood by laypersons. Ms. Levi-Pearl suggested that the consent document should include financial disclosure information for both the investigator and the sponsor.

Dr. Tzeng has seen no toxicities in her preclinical work with iNOS. She expressed an interest in seeing more preclinical data. For example, no studies have been conducted to look at the effects of iNOS in atherosclerotic vessels. Regarding the consent form, Dr. Tzeng asked that the use of angiography at 6 weeks after the stenting procedure be identified as part of the experimental design, since it is not the standard of care for patients receiving angioplasty and stent. She also questioned whether patients who might be better served by the standard of care, surgery, would be recruited into this study, and therefore, vulnerable lesions would not be treated appropriately.

Dr. Markert wondered whether rabbits that have developed atherosclerosis could be tested preclinically. Dr. Tzeng suggested that since proof of principle studies have already been conducted in the rodent, rabbits may not add important information. Dr. Tzeng suggested that more appropriate studies could be conducted using atherogenic or hyperlipidemic minipigs.

Dr. Cohen discussed the vague wording of the benefits section in the consent form and the need to clarify the difference between the potential for direct benefits and benefit to future patients and generalizable knowledge.

Continued Discussion and Investigator Response

Regarding the concern about using atherosclerotic animal models, Dr. Kuntz stated that the atherosclerotic pig model is difficult to reproduce. In the double injury model coupled with high-cholesterol chow feeding, the production of atherosclerotic plaques occurs rarely and inconsistently. Even when a narrowing of the arteries is achieved in pigs, histology does not show the characteristic plaque constituents, such as cholesterol clefts or calcium, found in humans.

Dr. von der Leyen addressed questions raised about transfection efficiency. The level of tranfection is sufficient to inhibit markers for proliferation. When proliferation was inhibited for the short term, restenosis was inhibited for the long term—4 weeks, 12 weeks, and 6 months. These studies indicate that a one-time application of the therapeutic substance is, with a high degree of probability, enough to prevent the proliferative response over a long time.

Regarding the pharmacology-toxicology studies with minipigs, Dr. von der Leyen explained that after extensive discussions with FDA reviewers, it was decided not to do these experiments with stent implantation because the stent implantation was likely to be a confounding factor in analyzing the tissues because of its propensity to induce vascular injury.

With respect to the consent form, Dr. Kuntz expressed his appreciation for the comments and agreed to make the suggested changes.

Dr. Kuntz explained the reasons the protocol was designed as a single vascular treatment. Such an approach allows a focus on any whole-body complications that might occur including myocardial infarction, elevations of cardiac enzymes, and other untoward events attributable to this procedure. Enrolling research participants who need treatment in two or more vessels might produce confounding outcomes.

Regarding the 6-week angiogram, Dr. Kuntz explained that this procedure has been recommended strongly by the FDA as a "watchdog angiogram" to uncover possible acute problems. Restenosis studies usually include a protocol-driven angiogram at 6 months to allow investigators to learn more about the restenosis process. The team would be pleased to use a non-invasive study if FDA determined that an alternative was appropriate. Dr. Kuntz concurred that the consent form should include information for the participant on the potential risks associated with the angiogram.

Dr. Kuntz explained that patient confidentiality will be maintained because, medical records would not be reviewed. In the field of interventional cardiology, potential research participants are not recruited by examining patient records. Investigators ask only those people to participate in trials who are referred to them because of a symptom-driven need for repeat revascularization.

At the request of Dr. Kuntz, Michael Curran, National Naval Medical Center, discussed his experience with the Infiltrator, which so far has been shown to be an efficient device for local specific delivery to the cell wall. The human clinical experience with this catheter includes treatment of 168 coronary artery lesions (142 research participants) in four separate studies. Experience to date has shown no increased risk of dissections above and beyond that seen with any other interventional device and no increased risk of myocardial infarction. Dr. Kuntz concluded with the explanation that lesion length determines length and number of Infiltrator applications.

Public Comments

No public comments were offered.

RAC Recommendations

Dr. Mickelson summarized the RAC recommendations:

- While the pig model with normal blood vessel does not completely represent the human disease of atherosclerosis, the RAC considered the model satisfactory to gather the preclinical data for the human trial.

- The RAC made several suggested changes to the informed consent document. The informed consent document should use a less technical language understandable to the research participants. The Introduction and Potential Benefits sections of the document should stress that the study is *experimental* and being carried out to ascertain the safety of the procedure. A clarifying statement should be added stating whether or not the investigators have any financial conflict of interest. The informed consent document should clarify that the study is limited to research participants requiring single vessel intervention, and that angiography performed six weeks after gene transfer is not a procedure required for the standard care of these research participants.

Committee Motion

As moved by Dr. Markert and seconded by Dr. Gordon, the RAC voted in support of conveying these recommendations to the principal investigator. The vote was 10 in favor, 0 opposed, and 2 abstained.

XV. FDA Perspective on the Development of an Adenoviral Standard/Stephanie L. Simek, Ph.D., CBER, FDA

The need for an adenoviral standard has been discussed since the first use of adenoviral vectors in cystic fibrosis clinical trials in 1993. At the December 1999 RAC symposium on adenoviral vectors, the RAC Adenoviral Safety and Toxicity Working Group recommended the development of qualitative and quantitative vector standards to compare adenovirus particles and infectious titers which would allow comparison of toxicities observed in different studies, both preclinical and clinical. FDA currently requests that dosing be based on particle number, but there is considerable inconsistency in that measurement. A more precise means of measuring viral particles would lead to better dose control, smaller dose increments, improvements in the determination of maximum tolerated dose, and the analysis of dose-related adverse events. The level of replication-competent adenovirus in each dose also needs to be determined more accurately. An adenoviral standard would serve as a reference to standarize both physical and biochemical measurements for virus particles and infectivity.

The Williamsburg BioProcessing (WBP) Foundation, in conjunction with FDA, industry and academia, held a conference on the development of an adenoviral vector standard on Oct. 5, 2000. The consensus of the participants of this conference was that a well-characterized standard for the use of adenoviral vector would be developed. A working group would be established with FDA taking the lead. FDA will be responsible for leading the process to evaluate and select group(s) to manufacture, characterize, and distribute the standard. The WBP Foundation will serve as a "facilitating entity" for the working group and FDA, and oversee the performance of each contractor involved in specific steps in standard development.

The FDA's role in this working group will be to review proposals for vector production; make recommendations for the selection of appropriate groups to manufacture, characterize, and distribute the standard; take the lead in setting the testing qualifications for the standard; collate data from standard testing; and provide guidance to the working group. FDA is also establishing an adenoviral research initiative to study the interaction of human and murine adenoviral vectors with viral receptors, and the effect of receptor interaction on viral tropism and pathogenesis.

Dr. Simek concluded by stating FDA's hope that development of a standard will bring about the production of more consistent, safer, quality adenoviral vectors; allow for the comparability of preclinical and clinical studies; and lead to the development of more defined regulatory policy.

XVI. Working Toward an Adenoviral Vector Testing Standard/Beth Hutchins, Ph.D., Canji, Inc.

Dr. Hutchins summarized the outcome of the Oct. 5, 2000 WBP meeting as the endorsement of the rapid development of a well-characterized adenoviral standard and the agreement that FDA should take responsibility for leading the process using a collaborative interactive working group approach. On November 8, 2000, the Working Group met for the first time, agreeing on its mission, how it will function, and defining the first set of activities and criteria for bids; a draft timeline for activities was also determined. The Working Group's mission will be to oversee development of a wild-type adenoviral standard, with the primary standard available by the end of 2001. The group will be responsible for identifying the process to evaluate and select appropriate groups to manufacture, characterize, and distribute the standards. This group will have wide representation from FDA, WBP Foundation, academic groups, contract manufacturers, testing companies, biotechnology and pharmaceutical companies and suppliers. Decisions made by this Working Group will be made available on Web sites, in journals and at public meetings, with information about the Working Group currently posted on the WBP Foundation Web site (www.wilbio.com).

The next steps for this Working Group will be to hold a meeting early in 2001 that will be open to the public and announced by FDA in the *Federal Register*. Subsequent to the meeting, a call will go out for bid proposals on production phase activities. Dr. Hutchins concluded by emphasizing the collaborative spirit of the effort aimed at developing products beneficial to patients.

RAC Discussion

In response to Dr. Greenblatt's question about the need for independent evaluation of the determination of standard particle number and infectious units, Dr. Hutchins replied that the plan is to utilize multiple laboratories, many of which have already expressed a desire to take part in this vector characterization. An ongoing stability characterization phase will be put into place to deal with the potential change over time in the number of particles in infectious units.

Dr. Hutchins emphasized that all the proposals submitted will be reviewed by the entire Working Group, so investigators should not include any information in those proposals that might be considered confidential.

Dr. Gordon expressed concern about the lack of financial commitment to the effort. Dr. Simek responded that each member of the Working Group is committed to this endeavor. Dr. Steven Bauer, FDA, added that FDA's participation will constitute an equal partnership— FDA will take the lead in a scientific and advisory capacity and make recommendations to the Working Group, which then will decide the final status of the vector. This Working Group will be considered a voluntary industry standard-setting group, which ensures the separation of financial interest from FDA.

Public Comments

No public comments were offered.

XVII. Discussion of Human Gene Transfer Protocol #0005-398: *A Phase I Study of a Tropism-Modified Adenoviral Vector for Intraperitoneal Delivery of Therapeutic Genes in Ovarian and Extraovarian Cancer Patients*

Principal Investigator:	Mack N. Barnes, M.D., University of Alabama, Birmingham
Other Investigators:	Ronald D. Alvarez, M.D., and Akseli Hemminki, University of Alabama, Birmingham
Sponsor:	N/A
RAC Reviewers:	Drs. Aguilar-Cordova, J. Gordon, and Macklin
Ad Hoc Reviewer:	Glen R. Nemerow, Ph.D., Scripps Research Institute

Protocol Summary

Gene transfer's potential as a cancer treatment depends on achieving efficient and specific gene delivery to cancer cells. The current methods used to evaluate gene transfer are invasive. At the Gene Therapy Program at the University of Alabama, Birmingham, program investigators have shown that adenoviral vectors can be manufactured to target cancer cells and accomplish enhanced gene delivery compared with unmodified adenoviral vectors. The tropism-modified vector, AdRGDTKSStr, is an Ad5-derived vector that encodes herpes simplex virus thymidine kinase (HSV-tk) and a somatostatin receptor. The tropism alteration is achieved by genetic modification of the adenoviral capsid proteins by insertion of an aeginin-glycine-aspartic acid (RGD) motif into the HI loop of the fiber knob. The RGD peptide is directed against integrins on the ovarian cancer cells which have been demonstrated in several studies to be overexpressed. Expression of the somatostatin receptor allows for noninvasive imaging of gene transfer using available radiologic methods. The investigators hypothesize that modifications to adenoviral vectors to increase their specificity and efficiency will allow enhanced entry into tumor cells and, thereby, an enhanced therapeutic effect in the treatment of ovarian cancer.

The Phase I protocol for ovarian and extraovarian cancer patients with persistent or recurrent disease has four goals:

> Determine the maximum tolerated dose of a three-amino-acid sequence (RGD sequence) genetically modified adenovirus encoding HSV-tk delivered into the abdominal cavity and given

in combination with IV ganciclovir in previously treated ovarian and extraovarian cancer patients. The spectrum of toxicities encountered with intraperitoneal delivery of this vector will be identified.

Determine the efficiency and specificity at which RGD genetically modified adenovirus accomplishes gene transfer to intra-abdominal ovarian cancer cells compared with normal cells.

Determine antibody response generated against the RGD-modified adenovirus encoding HSV-tk when administered intra-abdominally to patients with recurrent ovarian cancer.

Determine the ability to radiographically image adenoviral-encoded human somatostatin receptor after administration of a radiolabeled peptide (Tc-99m-P829) as a noninvasive method of evaluating gene transfer.

The experiments are expected to establish safety, provide an indication of the efficacy of this approach in human research participants with ovarian cancer, and allow the rapid evaluation of the its utility in future Phase II and Phase III trials.

Basis for Public Review

This protocol was determined to warrant public review by four RAC members because of its first use of a targeted adenoviral vector for *in vivo* administration. Dr. Gordon and Dr. Macklin were assigned to review the protocol in depth and they submitted written reviews as did *ad hoc* reviewer, Dr. Nemerow, to which the investigators responded in writing and during this meeting.

RAC Discussion

Dr. Gordon noted two novel aspects of the protocol: the adenovirus is modified to improve tropism for cancer cells and a gene encoding the somatostatin receptor is inserted. Dr. Gordon raised questions about the likelihood that the protocol's potential will be realized. In regard to the modified tropism, because the RGD motif would enhance vector uptake by any cell type expressing integrins, Dr. Gordon requested more information about whether transfer to tumor cells would be greater than to the many other types of cells present in the peritoneal cavity. Since imaging in the peritoneum would also be more complicated, he requested that additional experiments be done to determine whether there is sufficient resolution to identify tumor cells. He also questioned the need to administer ganciclovir in a phase I trial intended to determine maximal tolerated dose (MTD) of vector. The use of ganciclovir would be understandable if the MTD needed to be determined in the context of the adjuvant agent.

Dr. Aguilar-Cordova raised similar scientific concerns. He noted that it was difficult to compare results because different units for vector quantification were used (plaque-forming units vs. vector particles), that the testing requirements did not meet current standards, and that the dosages proposed were relatively low compared with those of other studies. Dr. Aguilar-Cordova suggested that the investigators not use the measure "plaque-forming units" but rather the more standard "viral particles" or "vector particles." He questioned the use of the word "therapy" throughout the consent form, the statement that research participants will be financially responsible for the imaging agent and the ganciclovir although neither is used commonly to treat ovarian cancer, and the listing of topothecan as an "alternative" rather than "standard" treatment for patients who have undergone cisplatin and not responded. He questioned the rationale for the proposed dosage since it is significantly lower than what has been used by other groups and since the vector is to be injected into the abdomimal cavity lower than that in their own preclinical animal studies.

Dr. Macklin's comments were focused on the ethical issues of recruitment, risk-benefit assessment, informed consent, among others. She asked whether there are any enhanced risks to individuals who are HIV-positive and therefore whether there is a reason to exclude them from this study. Her concerns with the consent document included the need for simplified language and the use of the word "therapy." She also suggested several issues that need to be clarified: to whom the term "your physician" refers; which risks are the results of the experimental procedures and which related to nonexperimental

ancillary procedures; and for which procedures and treatments research participants will have to pay. Dr. Macklin noted that most insurers will not cover procedures and related materials that are part of a research protocol. She pointed out that the potential benefits section of the consent document over-promises and uses significantly different terms from those used elsewhere in the protocol.

Dr. Nemerow raised questions about the efficacy and potential safety of the protocol. First, the protocol states that this was a virus specifically targeted for gene delivery uniquely to cancer cells but the current data indicate that, while the vector has enhanced tropism for cancer cells, it is not specifically targeted because it also still has the same tropism as the wild-type virus. He also asked whether the investigators had attempted to ascertain the level of transducing ability on normal cells and whether they have conducted biodistribution studies. Dr. Nemerow also noted that this protocol represents the first use of a targeted adenoviral vector in clinical gene transfer.

Dr. Markert questioned whether investigators would be able to find research participants who did not have pre-existing antibodies to adenovirus to assess therapeutic response to the vector in the absence of antibodies. She suggested including that the consent document should include the statement that the nuclear scan involves radiation and a request for autopsy. Dr. Markert also pointed out the value of establishing a DSMB and suggested inclusion of a point of contact at the institution who could discuss insurance coverage issues with potential participants.

Ms. Levi-Pearl suggested the use of subheadings and bullets to facilitate reading of the consent document, especially the procedures section. She also requested inclusion of financial disclosure and conflict-of-interest statements.

Dr. Ando asked whether the somatostatin receptor in the vector is biologically active and whether there had been an assessment of its potential to promote tumor growth. He also pointed out that the section on current Good Manufacturing Procedures (cGMP) is outdated.

Dr. Friedmann asked the investigators to discuss coxsackievirus and adenovirus receptor (CAR) independent attachment and what tissues may be targets *in vivo* in the peritoneum for CAR-independent attachment.

Dr. Gordon stated that participants should be informed about whether it is theoretically possible to enhance neoplastic growth of other cell types. He also noted that, since the investigators will be using a modified virus with modified tropism, they cannot be certain that response to ganciclovir will be the same as for an unmodified virus. It is possible that the ganciclovir adjuvant could be more toxic in this case.

Continued Discussion and Investigator Response

Dr. Barnes reported that the investigators have entered into discussions with the Rapid Access Intervention Development mechanism through the NCI for the development of a GMP-quality vector. Through their institution's award of a grant on ovarian cancer, the investigators have been able to provide funding for several of the corroborative laboratory studies.

In response to Dr. Gordon's concerns about the efficacy of the gene transfer with the RGD tropism modified vector, Dr. Barnes agreed that a specific antigen or target does not exist for ovarian cancer cells. He explained that the integrins were targeted because they are relatively overexpressed in ovarian cancer cells, according to reports in the literature and the investigators' laboratory findings. The toxicology and biodistribution studies that have been and will continue to be developed with FDA will play a critical role in addressing the question of what other tissues are trandsduced by this vector. In regard to imaging, results have been obtained from a mouse model in which the thyimidine kinase (TK) vector was instilled intraperitoneally as proposed for the human trials.

Regarding the use of ganciclovir, Dr. Barnes indicated that several *in vitro* and *in vivo* studies have demonstrated a therapeutic effect associated with TK gene transfer. As a researcher, he stated that he would be uncomfortable giving a research participant an adenoviral vector that encodes that therapeutic cassette without also supplying the prodrug that activates it.

Dr. Barnes explained that the low dosages of the virus chosen for this clinical trial are based on the safe doses used in the investigators previous trials. To test whether tolerated dose can be increased, the investigators have set up schedule of repetitive dosing.

In response to several RAC members' comments and suggestions about the informed consent document, Dr. Barnes agreed to limit the use of the term "therapy," explain the term "your physician" in relation to this protocol, delineate the risks associated with this experimental procedure and other procedures, and use simpler language.

Dr. Barnes indicated that the determination of who will hold the IND is being addressed at the investigators' institution. He further reported that neither he nor Dr. Alvarez has any financial interest in the vector product.

Dr. Akseli Hemminki, University of Alabama, Birmingham, responded to questions about the specificity of the targeted vector, possible effects of somatostatin receptor expression, and antibody response. Because the vector has enhanced infectivity rather than specificity, there could be increased uptake in non-tumor cells also. He indicated that ongoing toxicity and biodistribution studies will continue in order to help address this issue. The RGD motif was identified by *in vivo* phage display experiments using mice with tumors. Adenoviral transduction of primary tumor cells has been shown to be low, so the strategy is to increase transfer into tumors with this vector. Since the somatostatin receptor is expressed in some tumor cells, it may possibly affect tumor growth, but transduced cells could be destroyed by administration of ganciclovir to activate the TK gene. The vector is based on the adenovirus type 5 backbone, which is a natural pathogen of the upper respiratory tract. Thus, almost everyone has been exposed to it and has latent immune response to it. Neutralizing antibody studies are planned to be conducted on all research participants before, during and after the treatment.

RAC Recommendations

Dr. Mickelson summarized the following comments/recommendations offered by RAC members:

- The IBC may consider a higher physical containment level for the RGD modified adenoviral vector than the wild-type vector in the event that a replication-competent vector with extended host range is generated. Replication-competent adenoviruses are common recombination products found in adenoviral vector productions. Normally these recombinants are just viruses with the wild-type virus backbone; however, in this case, the recombinants would have an altered fiber/knob in the virions. A replication-competent adenovirus with an RGD motif in the fiber may have different pathogenic characteristics than wild-type adenovirus type 5. Thus, the containment required for production of this type of virus has to be evaluated.

- Vector titer should be expressed as the number of virus particles as opposed to the plaque forming units (PFU) used in the protocol.

- The vector product should be manufactured in accord with the current GMP regulations and current FDA regulations for adenovirus vectors.

- Further biodistribution studies should be performed with current GMP produced vector to determine potential target cells in the peritoneum that might be transduced by the tropism modified adenoviral vector.

- Immune response and toxicity data should be obtained 21 days after administration of the RGD modified adenoviral vector to immunocompetent mice.

- The somatostatin receptor should be further characterized for potential oncogenicity and methods for its further modification should be explored that would retain its ability to bind the radiolabel for imaging but not provide cells with a functional somatostatin receptor.

! Comments on the informed consent document: The informed consent document should be clarified that there will be no additional cost to the research participant for ganciclovir and imaging procedure required by the protocol, and that the investigators have no financial conflict of interest, and no testing for human immunodeficiency virus will be performed. The informed consent document should also state that alternative therapy such as chemotherapy is available, and should reduce the use of the word 'therapy" for gene transfer intervention. Clarification should be made as to who are "the physicians involved in this study." The informed consent document should include the name and phone number of the contact for research participant's questions, e.g., cost of research drugs and procedures. The document should use less technical language and be proofread by a layperson. It should also include statements about the use of radioactive isotope for imaging and the request for autopsy.

! The trial should receive adequate review of vector safety issues by the DSMB.

Committee Motion

As moved by Dr. Aquilar-Cordova and seconded by Dr.Gordon, the RAC voted to convey these recommendations to the investigators. The vote was 11 in favor, 0 opposed, and 1 abstention.

XVIII. Discussion of Human Gene Transfer Protocol #0010-419: *Intratumoral Injections of a Replication-Incompetent Adenoviral Vector Encoding a Factor VII Immunoconjugate To Induce a Cytolytic Immune Response Against Melanoma Tumors: A Pilot Trial*

Principal Investigator:	Albert B. Deisseroth, M.D., Ph.D., Yale University School of Medicine
Other Investigators:	Alan Garen, Ph.D., William Konigsberg, Ph.D., Yale University School of Medicine, and Yale Nemerson, M.D., Mount Sinai School of Medicine
Sponsor:	N/A
RAC Reviewers:	Drs. Ando and Chow and Ms. King
Ad Hoc Reviewers:	Nigel Mackman, Ph.D., Scripps Research Institute Jeffrey L. Platt, M.D., Mayo Clinic/Mayo Medical School

Protocol Summary

In the United States, the incidence of malignant melanoma is increasing more rapidly than any other cancer. The incidence rose from 1 in 1,500 in 1935 to 1 in 135 in 1987 and is projected to reach 1 in 75 in the year 2000. The cost of treating melanoma patients is $25 billion per year. Most successes in melanoma therapy have been achieved by surgery or immunotherapy, although there is no adequate treatment for advanced metastatic melanoma.

The principal purpose of the trial is to test the safety of administering intratumoral injections of a replication-incompetent adenoviral vector encoding a human Factor VII immunoconjugate (hFVII icon) to Stage IV melanoma patients. The hFVII icon is a bifunctional molecule composed of the human FVII targeting domain conjugated to the Fc region of a human IgG1 immunoglobulin as the effector domain. Factor VII binds with high specificity and affinity to the transmembrane receptor tissue factor (TF). Because TF is expressed on endothelial cells lining the luminal surface of the vasculature in solid tumors but not in nonproliferating normal tissues, it serves as a specific and accessible target for the tumor vasculature. Intratumoral injection of the adenoviral vector results in infection of cells in the injected tumor, which synthesizes and secretes the encoded icon into the systemic circulation. The blood-borne icon molecules are transported to the vasculature of all tumors, including uninjected tumors, and bind to TF on the tumor vasculature endothelial cells. Binding of the hFVII icon to TF induces a targeted cytolytic immune attack by components of the immune system that contain Fc receptors, resulting in destruction of the tumor vasculature. Because TF is also expressed on the cells of most types of tumors and because the tumor vasculature is leaky, the fvII icon also binds to TF on the tumor,

enhancing the cytolytic effect against the tumor. Patients will be monitored for signs of toxicity and also for changes in the size and number of their tumors.

Basis for Public Review

This protocol was determined to warrant public review by four RAC members because the use of the human FVII/hFc icon transgene raises significant potential safety issues that need to be addressed in preclinical studies. Dr. Ando, Dr. Chow and Ms. King were assigned to review the protocol in depth and submitted written comments as did *ad hoc* reviewers Dr. Mackman and Dr. Platt to which the investigators responded in writing and during this meeting.

RAC Discussion

Dr. Chow asked whether the human version of the mutated FVII, which has not been tested *in vivo* or *in vitro*, will work as safely and effectively as the mutated mouse version and whether the liver toxicity seen in those mice was reversible. She requested clarification regarding the criteria for stopping the trial.

Dr. Ando noted that the safety issues of tissue factor induction of disseminated intravascular coagulation (DIC) or bleeding should be evaluated *in vitro* in a human system and in nonhuman primates at a proportionate dose of adenovirus. He pointed out that bleeding or other thrombotic complications have been an issue with therapies involving tissue factor inhibition, and that this potential issue could be evaluated through careful dose escalation. Intracranial hemorrhage observed in a mouse needs to be evaluated further and could be a serious side effect. He also asked who will be making the material—Primedica or the Mount Sinai group.

Ms. King focused on ethical issues in the consent document. She expressed hope that the protocol had not received final approval from the IRB or the IBC because of continuing questions about whether enough preclinical work has been conducted to move into the clinical setting. Ms. King suggested that the investigators share a copy of her edits to the document with their IRB. Specific issues regarding the consent form included using different terms to describe the same concept, overstating benefits, and insufficient information in some sections. She also questioned what “withdrawal” from the study meant when the consent document states that research participants who withdraw will continue to be followed and clinical data will continue to be collected from those research participants’ medical records.

Dr. Platt suggested that if the investigators had further information about how the construct works (.ie. through an Fc-mediated killing process, by activating the complement system or by causing cells of the immune system to attack the tumor), the investigators could select participants who were immunocompetent in the appropriate way to allow the efficacy of this construct to be fully realized. He recommended that research participants should have kidney function on both sides to avoid possible renal failure since localized FVII deficiency can cause clot formation and bleeding in the kidneys.

Dr. Mackman expressed concern about chronically administering a potent anticoagulant. To determine whether spontaneous hemorrhages occur at different doses of the icon, he suggested additional preclinical studies using the rabbit whose clotting function more closely resembles human. Dr. Mackman suggested that rather than treatment with red cells alone the protocol include packed red cells with FVIIa. He stated that it is critical to establish doses that will kill the tumor without inducing hemorrhage. He said that the preliminary data did not establish with certainty that the dose in the protocol would not induce hemorrhages.

Dr. Markert suggested that patients who are enrolled should have natural killer (NK) cells. She suggested that investigators test how long expression lasts in the serum of immunocompetent mice. Dr. Markert also suggested that a DSMB should be established.

Dr. Aguilar-Cordova also expressed concern about the potential dangers of hemorrhaging or disseminated intravascular coagulation (DIC), especially since DIC has been a problem with adenovirus-derived vectors in general.

Dr. Macklin expressed concern about the statement in the consent form that research participants will be responsible for medicines to treat side effects of the therapy. She questioned the ethics of charging research participants for medicines that are needed to ameliorate a condition that is caused by the research. Dr. Greenblatt suggested participant's insurance company will pay for treating side effects. Dr. Macklin also requested clarification about research participants' financial responsibility for tests related to the clinical trial.

Investigator Response

Regarding the concern about the risks of DIC and bleeding, Dr. Garen responded that they regard DIC as the more serious problem, and they have been able to reduce the effectiveness of the coagulation function of FVII by putting a single amino acid substitution into the active site.

Regarding concerns about bleeding that occurred in the mice, Dr. Garen pointed out that the mice were injected intravenously. The IV route produces a very different result from the intratumoral (IT) route proposed for this protocol. IV injection produces an increase of circulating icon molecule of at least one order of magnitude higher than the IT route, and the likelihood of bleeding is proportional to the amount of circulating icon.

Dr. Garen clarified that the mouse FVII is capable of binding to both human and mouse tissue factors; in the mouse experiments, murine FVII was used, but in the clinical trials, human FVII will be used. With regard to the possible immunogenicity of the mutated FVII, he cited a clinical study in which hFVII had been rendered inactive for coagulation by modification of the active site, and then injected into human volunteers. No immune response was seen against this FVII molecule which was more extensively modified than the mutated FVII being used in this protocol.

In vitro experiments to determine the mechanism indicated that both NK cells and complement components may be involved in the anti-tumor response. In response to a question from Dr. Greenblatt about species specificity, Dr. Garen replied that the investigators were not able to test the human molecule in other species because the hFVII molecule does not bind well to any of the primate or other animal tissue factors, and testing of anything human in a primate will produce an immune response that will complicate interpretation of the results.

Dr. Deisseroth responded to safety concerns by explaining that the level of inactivated FVII injected into the mice was seven times the proposed amount to be injected in human participants. Since no toxicities occurred in the mouse studies, the human trials should be safe. Dr. Deisseroth stated that no elevations were observed above the upper limit of normal for aspartate transaminase levels or no changes in liver histopathology were observed. In response to Dr. Chow's concerns about potential toxicities, the investigators are now proposing that research participants in the third and fourth cohorts of the four-cohort dose escalation be treated one at a time.

Regarding questions about the informed consent document, Dr. Deisseroth explained that the purpose of the withdrawal statement was to reassure patients that they could withdraw from the study without an adverse effect on their relationship with the hospital. He clarified what the stopping rules were and said that investigators have stipulated that the trial will be stopped if any one patient dies. An external monitoring board will review all the relevant data to determine whether the death may be associated with the use of the icon. Dr. Deisseroth noted about costs to the patient that the statement in the consent document is a standard policy at Yale University, but he clarified that an agreement is reached with the insurer prior to enrollment that all complications of the study participation will be covered. For research participants who have no insurance, a fund at Yale New Haven Hospital can be used on a case-by-case basis.

Dr. Deisseroth stated that research participants will be screened for NK cell levels and complement levels as several members suggested.

Dr. Deisseroth summed up the investigators' recognition of the risks associated with the protocol described what is being done through the use of exclusion criteria to reduce those risks. Individuals will

be excluded if they have any condition that might increase the likelihood of the immunoconjugate binding to normal endothelial cells. This includes people with atherosclerotic disease, viral infections, immune complex disease, or bleeding disorders. The dose escalation with sequential treatment at the higher doses and the stringent stopping rules based on coagulation assays will provide further safeguards.

Public Comments

No public comments were offered.

RAC Recommendations

Dr. Mickelson summarized the following comments and recommendations offered by RAC members:

! To address the safety concerns of abnormal bleeding and DIC, the RAC recommended consideration of further safety testing with the adenovirus expressing the immunoconjuage (icon) in larger animals to evaluate the potential for systemic and localized bleeding in non-tumor sites, if the species specificity of the human icon allows such an assessment.

! The safety data of animal and tissue culture testing should be obtained on the actual vector construct to be used in humans. The data of *in vitro* testing for icon using human plasma on the prothrombin time is desirable. The RAC noted that most previous safety testings were performed in mice using an adenovirus expressing the murine version of the mutated icon.

! Most bleeding and DIC safety studies were performed in mice with severe combined immunodeficiency (SCID); a more relevant model would be represented by immunocompetent mice bearing a syngeneic tumor.

! The RAC recommended studies of the potential immunogenicity of the icon such as assays for a neutralizing antibody. This could have significance towards a second round of transduction.

! The RAC recommended a sequential dose escalation scheme for the study design, i.e., for the 3rd and 4th cohorts, one patient be enrolled at a time.

! The RAC recommended a more stringent stopping rule, i.e., stop the trial if there is one participant death due to excessive bleeding rather than applying the standard three-death rule.

! Biodistribution data should be obtained on mouse experiments to ascertain if there is any unintended icon expression outside the tumor target. Since adenovirus has been found in liver after intratumoral injection, further biodistribution studies should be performed to determine sites of icon distribution and expression outside the intended tumor target.

! Due to safety concerns regarding the potential for localized factor VII deficiency causing bleeding and clotting in the kidney, the eligibility criteria should include only research participants with adequate renal function in both kidneys. Evaluation of normal kidney function should include a radionuclide scan of the kidneys to confirm perfusion and function of both kidneys.

! Research participants should be tested for complement level and NK cell function since the antitumor strategy of icon gene transfer and cell-mediated immunity could involve one or more of these systems.

! The language of the informed consent document should be clarified in regard to the research participant's responsibility for costs related to side effects of the intervention. The investigators assured the RAC that all research participants will be pre-certified for insurance coverage, and a Yale University special fund will be available for those without adequate insurance. Information for the latter payment should be provided as part of the consent process and described in the informed consent document.

! The language of the informed consent document is overly scientific and not comprehensible to an average lay reader. Suggested changes to the informed consent document have been provided to the investigators for their consideration.

Committee Motion

As moved by Dr. Markert and seconded by Dr. Ando, the RAC voted in support of conveying these recommendations to the investigators. The vote was 10 in favor, 0 opposed, and 2 abstained.

XIX. Discussion of Human Gene Transfer Protocol #0010-426: *A Phase I Study of Intratumoral Injections of OCaP1 for Metastatic or Locally Recurrent Prostate Cancer—Part 1: Dose Finding, Part 2: Index Lesion Escalation*

Principal Investigator:	Thomas A. Gardner, M.D., Indiana University
Sponsor:	DirectGene, Inc., represented by Dale VanderPutten, M.B.A., Ph.D.
RAC Reviewers:	Drs. Breakefield and Chow and Ms. Levi-Pearl
Ad Hoc Reviewer:	Glen R. Nemerow, Ph.D., Scripps Research Institute

Protocol Summary

Prostate cancer is estimated to be the leading male cancer diagnosis and the second most common cause of male cancer death in the United States. Prostate cancer detected in early stages can be treated successfully by surgery or radiation. However, 10 to 15 percent of patients will have metastatic cancer at the time of diagnosis. In patients undergoing removal of the prostate, residual cancer cells remain in 20 to 30 percent. Thus, a significant number of patients are at risk for a local regrowth of prostate cancer. Metastatic prostate cancer may subsequently develop in some patients after surgery or radiation. The most common locations for the spread of prostate cancer are the bones and lymph nodes. Although, removing or blocking the male hormone testosterone can slow the growth of prostate cancer, no effective therapy is available for patients whose prostate cancer recurs or metastasizes. New therapeutic approaches for these patients are needed.

This protocol uses an adenovirus to specifically target and kill prostate cancer, including cancer that has spread to the bone and lymph nodes. The Ad-mOC-E1a virus (OCaP1) has been altered to confine the virus to prostate cancer tumors. To kill prostate cancer cells while leaving normal tissue unharmed, the targeting of the virus is achieved by the controlled expression of the adenoviral E1a gene by the osteocalcin (OC) promoter that functions in cells that have the ability to deposit calcium (e.g. bone, prostate cancer cells). The OC promoter is primarily active during childhood and adolescence when bones are growing. Prostate cancer cells have properties similar to growing bones. The protocol is designed to demonstrate the ability of Ad-mOC-E1a to safely target and kill prostate cancer cells.

In the first group of participants, a single tumor will be injected with one of four doses of Ad-mOC-E1a. This will be followed by an escalation in the number of tumors injected (from two to five) in a different group of research participants.

The primary objective of this study is to demonstrate whether a single direct injection of Ad-mOC-E1a into one to five tumors is safe. The feasibility and potential effectiveness of this approach will be evaluated through biologic and radiologic evaluations.

Basis for Public Review

This protocol was determined to warrant public review by three RAC members for the following reasons: safety issues involving a replication competent virus carrying a novel OC promoter and the potential replication of this type of virus in normal tissues. Dr. Breakefield, Dr. Chow and Ms. Levi-Pearl were assigned to review the protocol in depth and submitted written reviews, as did *ad hoc* reviewer, Dr. Nemerow, to which the investigators responded in writing and during this meeting.

RAC Discussion

Dr. Breakefield expressed concern that insertion of a tissue specific promoter into a viral backbone may alter its specificity, and the TK data from a replication incompetent virus were not definitive on this issue. Another major concern is whether virus could spread to other individuals, particularly children with developing bones. Dr. Breakefield requested that the investigators screen stool and saliva in addition to blood and urine for presence of the virus. She questioned whether the virus could find a haven in other tissues where it would then replicate and, therefore, dramatically increase viral shedding.

Dr. Chow suggested that investigators test several additional cell lines to ensure that the virus does not replicate in different body sites. Because this virus is replication competent and because low levels of messages were found in the mouse in many different tissues, investigators should provide more evidence that the virus only replicates in the prostate tumors.

Dr. Nemerow remarked that this trial has substantial merit built on valuable prior experience. He wondered why a mouse OC promoter was used rather than a human promoter and what differences could be expected in terms of expression. Because the OC promoter has a vitamin D response element, he also asked whether dietary factors might be an issue for some research participants. He also asked which of the three different human OC promoters are being used in the vector. Regarding safety issues, Dr. Nemerow noted that data suggest that there is replication in OC-negative cells.

Ms. Levi-Pearl complimented the investigators on the quality of the consent document and suggested that investigators add language to indicate that participants in the study will be notified of any untoward events that occur within the trial that would influence their desire to continue in the study.

Dr. Aguilar-Cordova expressed concern about the potency of the promoter compared with the wild-type adenovirus E1 promoter, especially in bone cells. He also noted, in regard to how well the vector targets, that other replication conditional vectors are retarded in growth initially in non-target cells but, given enough time, they do eventually proliferate in non-target cells too.

Dr. Macklin endorsed Ms. Levi-Pearl's comment about the consent document and stated that it was one of the best forms she has seen. She did, however, think the document overstated the potential benefits to the research participants and that the potential benefits should be stated so that they match precisely what is written elsewhere in the protocol. Dr. Macklin recommended that the language of the consent needs to be simplified.

Dr. Gordon was less concerned about replication than efficacy since the virus should be cleared by an immune response, thus, would no longer kill cells. Dr. Nemerow suggested that it was probably a race between the virus and the immune system.

Dr. Mickelson agreed with Dr. Aguilar-Cordova's point that it is possible that the adenovirus might replicate better in osteoblasts and, therefore, that additional tests related to replication should be performed.

Investigator Response

Dr. Vander Putten addressed the questions about the promoter. The mouse OC promoter was chosen because it does not have the vitamin D regulatory element, is two-fold less active in humans than the human promoter, and is tightly regulated.

In response to Dr. Breakefield's request to check stool and saliva in addition to blood and urine for the virus, Dr. Gardner agreed to check at least the first several research participants for evidence of viral shedding.

Regarding Dr. Chow's suggestion about checking additional cell lines, Dr. Gardner noted that numerous studies currently under way are testing additional cells, so that much additional information will be learned about this promoter in the near future.

With regard to a comment of Dr. Gordon about an immune response clearing virus before it can kill tumor cells, Dr. Gardner stated that, unlike the OC TK replication incompetent vector, this vector has an intact E3, which may potentially help the virus evade the immune response.

Dr. Gardner explained that the investigators determined dose by viral particles, not multiplicities of infection. The dose is based on safety information from other replication-competent vectors as well as experience with their own OC TK vector.

With respect to the consent document, Dr. Gardner agreed to change the benefits section as suggested. He acknowledged that a great deal of expert input was obtained in writing the consent including a scientific advisory board with a great deal of experience in gene transfer trials.

Dr. Mickelson raised another question about the potency of the OC promoter compared with the E1 promoter in bone cells. Dr. Gardner responded that, by aiming the virus with its promoter specificity at the tumor, the investigators hope to enhance the efficacy and potentially obtain the same level of safety as that exhibited by the wild-type virus. Although osteoblastic cells have higher levels of OC, those cells are replaced randomly approximately every 3 months. Even if every osteoblastic cell were wiped out, the body would repopulate itself with progenitor cells.

Public Comments

No public comments were offered.

RAC Recommendations

Dr. Mickelson summarized the following recommendations and comments offered by RAC members:

- Monitoring of the research participants for virus shedding should include saliva and stool as well as urine and semen for extended periods after injection in order to observe any emergence of replicating virus. At least for the initial set of research participants, the RAC requests that the research participants be restricted from contact with other individuals after administration of the vector until no more virus shedding is detected, and a bone scan be performed to monitor possible bone loss due to the vector administration.

- To further examine the specificity of the OC promoter to limit viral replication to prostate tumor cells, Ad-mOC-E1A vector should be compared to a vector with the viral E1A promoter to test for toxicity in normal human cells in culture such as neural cells, e.g., NT2 line, hepatocytes, haematopoietic cells and osteoblasts.

- The readability of the informed consent document was excellent. However, the Investigational Procedures section can be clarified by the addition of subheadings. The potential benefits as outlined in the informed consent document should match the language employed in the clinical protocol. The informed consent document should state the commitment to inform the research participants promptly of any serious adverse events that may influence their willingness to continue to participate in the experiment. The potential for spreading of the replication-competent virus to individuals coming in contact with the research participants should be stated in the informed consent document including the possibility that, if this event occurs, the most sensitive ones would be fetuses, children, adolescents and immune-compromised individuals.

Committee Motion

As moved by Dr. Markert and seconded by Dr. Gordon, the RAC voted in support of conveying these recommendations to the principal investigator. The vote was 6 in favor, 0 opposed, and 0 abstained.

XX. Proposed Action To Amend the *NIH Guidelines*' Requirements for Serious Adverse Event Reporting (SAER)/Dr. Patterson

Dr. Patterson noted that recent events in gene transfer studies have raised concerns and questions about the scope of adverse events (AEs) reported to NIH, the adequacy of Federal and local review and analysis of AEs, and the best way to communicate safety information. Proposals for change have come from Congress, bioethicists, advocacy groups, the biotechnology industry, and the scientific community.

Dr. Patterson summarized the proposed action's four key topics: scope and timing of SAER; public access to safety information; protection of research participant privacy in SAER; and review, assessment and communication of safety information. The first proposed change would require expedited reporting for those serious adverse events (SAEs) that are unexpected and considered possibly associated with the use of gene transfer products. The proposed change also provides timeframes for expedited reporting and definitions of serious, associated and unexpected adverse events. Under the proposal, other reportable SAEs would be included in annual reports. The second proposed change would clarify that SAERs submitted to NIH may not be classified as confidential information and that trade secret or other commercial confidential information should not be included in SAERs. The third proposed change adds specific language to the NIH Guidelines to prohibit the submission of individually-identifiable patient information in SAERs. The fourth change is the establishment of a working group of the RAC, to be known as the NIH Gene Transfer Safety Assessment Board, that will be responsible for the review and analysis of SAERs and other relevant safety information to the RAC and information will, thereby, be disseminated to the scientific and patient communities and the public.

The NIH Gene Transfer Safety Assessment Board (GTSAB) will review and analyze SAEs and cumulative toxicity data across all gene transfer trials, identify trends and/or single events, and report findings, conclusions, and aggregated trend data for public discussion at RAC meetings. The Board will serve in an advisory capacity, and its authority will not supersede or replace the FDA's responsibility to respond to SAEs. Composition of this Board will be approximately 15 members, including experts in relevant fields, two RAC members, NIH staff members, an FDA liaison, and *ad hoc* members added as needed depending on the topic. The Board will meet quarterly in closed session prior to a RAC meeting, providing reports to the RAC and OBA and, thereby, to the public. The Board will be staffed by OBA.

At the next meeting of the RAC, the public comments to the proposal will be considered and the RAC will be asked to make recommendations to the NIH director about whether the proposal should be implemented. The NIH Director makes the final decision regarding implementation of the proposed action.

RAC Discussion

Dr. Noguchi pointed out the importance of ensuring that GTSAB members' potential conflicts of interest are carefully addressed. In response to Dr. Noguchi's question about safety reports containing trade secret information, Dr. Patterson responded that NIH at present is interpreting "trade secret" and "commercial confidential" to be a detail of the manufacturing process. NIH recognizes that there may be instances in which such details may have a bearing on a SAE; under those circumstances, those aspects of the information submitted would be kept confidential. In general, however, NIH would expect safety reports to be devoid any trade secret information.

Dr. Gordon commented on the importance of the public access to safety information. Such information is especially critical for members of the public considering participating in a trial similar to one in which

there has been report of an AE. Dr. Patterson pointed out that the Board will also be able to request additional information if necessary.

Dr. Friedmann raised a question about the length of time between meetings of the Board and the RAC. Dr. Patterson explained that Board meetings would be scheduled in sequence with RAC meetings so that reports to the RAC would be timely. Dr. Macklin expressed some concern that expected SAEs would no longer have to be reported on an immediate basis. Dr. Jay Siegel, FDA, reported that in FDA's experience annual reports of expected events provides sufficient oversight.

Dr. Siegel commented that FDA was supportive of the establishment of the Board and that it would be important to ensure that it functions in a complimentary value-added way. Dr. Siegel asked whether data from studies not within the purview of the RAC, for example pox or plasmid vectors used for vaccines for microbial antigens, would be integrated into this Board's conclusions. Dr. Patterson agreed that some of the scientific and safety issues raised by these classes of products would be germane and would provide an important backdrop to the interpretation of human gene transfer studies. She stated that the agencies have initiated discussions on how this type of information should be shared. Dr. Mickelson and Dr. Gordon affirmed the importance of the Board having access to data that could assist and enhance its work. Through Ms. Levi-Pearl, Ms. King conveyed the view that this Board should have the authority to request more frequent or more extensive AE reporting for particular protocols or classes of protocols when necessary.

In response to a comment of Dr. Gordon, Dr. Patterson agreed that the new database would be an important tool for the Board.

Public Comment

J. Tyler Martin, Sr., M.D., Valentis

Dr. Martin expressed concern that operational support for the Board will involve a great deal of work to collect and evaluate SAEs and avoid duplication. Tasks such as auditing and coding will require special skills. He also expressed concern that some data elements that must be reported have the potential to compromise patient confidentiality, for example, the date and site of the trial could indirectly provide clues to the patient's identity. The timing of the SAEs relative to the gene transfer should only be included. Dr. Martin recommended clarification of the section of the proposal that discusses what may be delegated to the sponsor and the sponsor's role in relation to the investigator. He indicated that Valentis would provide additional comments in writing.

Michael Losow, Biotechnology Industry Organization (BIO)

Mr. Losow stated that BIO agreed with the NIH's efforts to harmonize the NIH and FDA SAER systems but is concerned with other aspects of the proposal. Rather than creating a working group of the RAC to analyze SAEs, BIO recommended that FDA create a DSMB to receive and review SAE reports for the RAC. This would ensure the protection of confidential patient or company information. As gene therapy moves from the research laboratory to the development of therapeutic products for the commercial market, the RAC's important role should be to facilitate public discussion of the ethical and social issues surrounding gene therapy. BIO will be submitting more detailed comments to NIH.

Deanna Frost, Ph.D., Western Institutional Review Board

Dr. Frost asked whether Board reports would be transmitted to IRBs and IBCs. She also suggested that as necessary the Board or the RAC recommend specific language that should be added to consent documents in light of the safety analysis.

RAC Discussion

Dr. Patterson offered two clarifications in response to Mr. Losow's comments. One of the reasons that the Board was proposed to be situated at NIH in association with the RAC is because NIH believes that public access to safety information is critical to move the field forward. If the Board were situated at FDA, most of the information could not be made public. She reiterated that the Board will be composed of two representatives from the RAC, liaisons from FDA, and experts drawn from pertinent disciplines to provide expertise needed for accurate analysis of clinical trial data and preclinical pharmacology-toxicology studies.

Dr. Siegel offered his personal view (not FDA's) that the Board will need to be carefully implemented to be sure it does not duplicate FDA's SAE analysis responsibilities.

In response to Dr. Frost's questions, Dr. Patterson explained that the details of how the Board will function remain to be worked out, but NIH is eager to hear from local review committees about what type of information would be useful to them and how the Board should communicate that information to them. She noted that when the Board reports to the RAC, an opportunity exists for the RAC and OBA to send recommendations to IRBs. Dr. Noguchi also suggested that the Office for Human Research Protections have a liaison position on this board, since that Office has a direct relationship with IRBs.

XXI. Chair's Closing Remarks/Dr. Mickelson

Dr. Mickelson reported that the scope and applicability working group met to continue assessing the need for modification to the scope of the NIH Guidelines. The group's efforts will continue and recommendations will be made to the full committee at the March 2001 RAC meeting.

XXII. Adjournment/Dr. Mickelson

Dr. Mickelson adjourned the meeting at 5:10 p.m. on December 15, 2000.

[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.]

Amy P. Patterson, M.D.
Executive Secretary

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

Date:

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Chair

Attachment I
Committee Roster

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Attachment II
Attendees

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Mack N. Barnes, University of Alabama, Birmingham
Cindy Beart, citizen
Jennifer A. Beart, easydiabetes.com
Robert W. Beart, Jr., University of Southern California
Martin R. Berwitt, Planet Productions
Mehmet Betil, Karma
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Flavia Borellini, Cell Genesys
Joseph Bruder, GenVec
Andrew Byrnes, U.S. Food and Drug Administration
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Joy A. Cavagnaro, Access Bio
Yung-Nien Chang, Virxsys
Heather Chapman, Cornell University
John Chapman, U.S. Patent Office
Janice Chappell, Direct Gene, Inc.
Nancy Chew, Regulatory Affairs
Shirley Clift, Cell Genesys
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Attachment III
Abbreviations and Acronyms

ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AST	aspartate transaminase
BIO	Biotechnology Industry Organization
CAR	coxsackievirus and adenovirus receptor
CBER	Center for Biologics Evaluation and Research
CMV	cytomegalovirus
DIC	disseminated intravascular coagulation
DNA	deoxyribonucleic acid
dnG1	dominant negative cyclin G1
DSMB	Data and Safety Monitoring Board
EGF	epidermal growth factor
FDA	U.S. Food and Drug Administration
β-FGF	fibroblast growth factor
FVII	Factor VII
FVIII	Factor VIII
GMP	Good Manufacturing Procedures
GTR	gene transfer research
GTSAB	Gene Transfer Safety Assessment Board
hFVII	human Factor VII
HIV	human immunodeficiency virus
HSV-tk	herpes simplex virus thymidine kinase
IBC	Institutional Biosafety Committee
IND	investigational new drug
iNOS	inducible nitric oxide synthase
IBC	Institutional Biosafety Committee
IRB	Institutional Review Board
IT	intratumoral
IV	intravenous
JEB	junctional epidermolysis bullosa
MLV	murine leukemia virus
MTD	maximal tolerated dose
NCI	National Cancer Institute
NIH	National Institutes of Health
NIH Guidelines	*NIH Guidelines for Research Involving Recombinant DNA Molecules*
NK	natural killer
NO	nitrous oxide
OBA	Office of Biotechnology Activities (formerly ORDA, Office of Recombinant DNA Activities)
OC	osteocalcin
OHRP	Office of Human Research Protections
PBL	peripheral blood lymphocytes
PCR	polymerase chain reaction
PFU	plaque forming units
PI	principal investigator
RAC	Recombinant DNA Advisory Committee
RCR	replication-competent retrovirus
RGD sequence	arginin-glycine-aspartic acid sequence
SCID	severe combined immunodeficiency
SAE	serious adverse event
SAER	serious adverse event reporting
TF	transmembrane receptor tissue factor

TK	thymidine kinase
USC	University of Southern California
VEGF	vascular endothelial growth factor
WBP Foundation	Williamsburg BioProcessing Foundation