RECOMBINANT DNA ADVISORY COMMITTEE

Minutes of Meeting

December 3-4, 2008

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

Contents

I. Day 1 Call to Order and Opening Remarks 2

II. Minutes of the September 9-10, 2008, RAC Meeting 2
A. Committee Motion 1 2

III. Followup on *NIH Guidelines for Research Involving Recombinant DNA Molecules:* Human H2N2, Reconstructed 1918 H1N1, and Highly Pathogenic Avian Influenza H5N1 Viruses 3
A. RAC Discussion 4
B. Public Comment 5

IV. Discussion of Human Gene Transfer Protocol #0808-946: Phase I Trial of Intratumoral Injection of Vesicular Stomatitis Virus Expressing Interferon Beta in Patients with Hepatocellular Carcinoma 5
A. Protocol Summary 5
B. Written Reviews by RAC Members 6
C. RAC Discussion 6
D. Investigator Response 7
1. Written Responses to RAC Reviews 7
2. Responses to RAC Discussion Questions 8
E. Public Comment 9
F. Synopsis of RAC Discussion and RAC Observations and Recommendations 9
G. Committee Motion 2 10

V. Gene Transfer Safety Assessment Board Report 11

VI. Discussion of Human Gene Transfer Protocol #0808-942: A Phase Ib, Multicenter, Single-Blinded, Placebo-Controlled, Sequential Dose-Escalation Study to Assess the Safety of Topically Applied AG013 in Subjects Receiving Induction Chemotherapy for the Treatment of Cancers of the Head and Neck 11
A. Protocol Summary 11
B. Written Reviews by RAC Members 12
C. RAC Discussion 13
D. Investigator Response 13
1. Written Responses to RAC Reviews 13
2. Responses to RAC Discussion Questions 14
E. Public Comment 15
F. Synopsis of RAC Discussion and RAC Observations and Recommendations 15
G. Committee Motion 3 16

VII. Discussion of Human Gene Transfer Protocol #0808-934: A Phase I, Open-Label Study of the Safety, Tolerability, and Therapeutic Activity of JVRS-100 Cationic Lipid-DNA Complex in Patients with Chronic Hepatitis C Infection Who Relapsed After Receiving Interferon-Ribavirin Treatment
AND
Discussion of Human Gene Transfer Protocol #0808-936: A Phase I Trial of the Immunostimulant JVRS-100 for the Treatment of Patients with Relapsed or Refractory Leukemia 16
A. Summary of Protocol #0808-934 16
B. Written Reviews of Protocol #0808-934 by RAC Members 17
C. Summary of Protocol #0808-936 18
D. Written Reviews of Protocol #0808-936 by RAC Members 18
E. RAC Discussion of Protocols #0808-934 and #0808-936 19
F. Investigator Response 19
1. Written Responses to RAC Reviews of Protocols #0808-934 and #0808-936 19
2. Responses to RAC Discussion Questions for Protocol #0808-936 20
G. Public Comment on Protocols #0808-934 and #0808-936 20

H. Synopsis of RAC Discussion and RAC Observations and Recommendations 20
1. Protocol #0808-934 20
2. Protocol #0808-936 21
I. Committee Motion 4 22

VIII. Day 1 Adjournment 22

IX. Day 2 Call to Order and Opening Remarks 22

X. Update on Allogeneic Bone Marrow Transplantation for X-SCID 22
A. Introduction 22
B. Presentations 22
C. RAC Discussion 23
D. Public Comment 24

XI. Discussion of Human Gene Transfer Protocol #0808-950: Gene Therapy for SCID-X1 Using a Self-Inactivating (SIN) Gamma-retroviral Vector 25
A. Protocol Summary 25
B. Written Reviews by RAC Members 26
C. RAC Discussion 27
D. Investigator Response 28
1. Written Responses to RAC Reviews 28
2. Responses to RAC Discussion Questions 29
E. Public Comment 30
F. Synopsis of RAC Discussion and RAC Observations and Recommendations 30
G. Committee Motion 5 31

XII. Closing Remarks and Adjournment 31

Attachment I. Recombinant DNA Advisory Committee Roster A-I-1
Attachment II. Public Attendees A-II-1
Attachment III. Abbreviations and Acronyms A-III-1

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

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

December 3-4, 2008

The Recombinant DNA Advisory Committee (RAC) was convened for its 115th meeting at 9:30 a.m. on December 3, 2008, at the National Institutes of Health (NIH) Conference Center, 5635 Fishers Lane, Rockville, Maryland. Dr. Howard Federoff (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public from 9:30 a.m. until 4:45 p.m. on December 3 and from 8:00 a.m. until 12:50 p.m. on December 4. The following individuals were present for all or part of the December 2008 RAC meeting.

Committee Members

David A. Alland, University of Medicine and Dentistry of New Jersey *(via teleconference)*
Jeffrey S. Bartlett, Nationwide Children's Hospital/The Ohio State University
Michael J. Buchmeier, University of California, Irvine
Hildegund C.J. Ertl, The Wistar Institute
Hung Y. Fan, University of California, Irvine
Howard J. Federoff, Georgetown University Medical Center
Jane Flint, Princeton University *(via teleconference)*
Jeffrey P. Kahn, University of Minnesota *(present on Day one only)*
Joseph A. Kanabrocki, The University of Chicago
Louis V. Kirchhoff, University of Iowa
Eric D. Kodish, The Cleveland Clinic Foundation
Bernard Roizman, The University of Chicago
Prediman K. Shah, Cedars-Sinai Medical Center *(via teleconference on Day one)*
Robyn S. Shapiro, Medical College of Wisconsin
Nikunj V. Somia, University of Minnesota, Twin Cities *(present on Day one; via teleconference on Day two)*
Scott E. Strome, University of Maryland
David A. Williams, Children's Hospital Boston/Harvard Medical School *(present on Day one only)*
James R. Yankaskas, The University of North Carolina at Chapel Hill
John A. Zaia, City of Hope

Office of Biotechnology Activities (OBA)

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

***Ad Hoc* Reviewers and Speakers**

Mitesh J. Borad, Mayo Clinic
Rebecca H. Buckley, Duke University Medical Center
David F. Claxton, Penn State Hershey Cancer Institute
Morton J. Cowan, UCSF Children's Hospital
John McHutchison, Duke University Medical Center
Barbara Murphy, Vanderbilt University
Luigi D. Notarangelo, Children's Hospital Boston
Richard J. O'Reilly, Memorial Sloan-Kettering Cancer Center
Naomi Rosenberg, Tufts University
Adrian Thrasher, Institute of Child Health, London, England

[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.

John Treanor, University of Rochester Medical Center *(via teleconference)*
Richard G. Vile, Mayo Clinic

Nonvoting Agency Representatives

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

NIH/OD/OBA Staff Members

Linda Gargiulo
Bob Jambou
Laurie Lewallen
Maureen Montgomery
Marina O'Reilly
Lisa Parker
Gene Rosenthal
Tom Shih

Others

There were 73 attendees at this 2-day RAC meeting.

Attachments

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

I. Day 1 Call to Order and Opening Remarks

Dr. Federoff, RAC Chair, called the meeting to order at 9:30 a.m. on December 3, 2008. Notice of this meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (*NIH Guidelines*) was published in the *Federal Register* on November 6, 2008 (73 FR 66053). Issues addressed by the RAC at this meeting included a report from the Gene Transfer Safety Assessment Board (a subcommittee of the RAC), public review and discussion of five protocols, an update of the RAC's Biosafety Working Group's (a subcommittee of the RAC) consideration of changes to the *NIH Guidelines* regarding human H2N2, 1918 H1N1 influenza viruses and highly pathogenic avian influenza H5N1, and an update on allogeneic bone marrow transplantation for X-SCID.

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

II. Minutes of the September 9-10, 2008, RAC Meeting

RAC Reviewers: Drs. Shah and Yankaskas

Dr. Yankaskas stated that the minutes accurately reflected the proceedings of the meeting, with one minor word modification that had been submitted previously.

A. Committee Motion 1

Approval of the September 9-10, 2008, RAC meeting minutes was moved and seconded. The RAC voted unanimously by voice vote to approve the September 9-10, 2008, RAC meeting minutes.

III. Followup on *NIH Guidelines for Research Involving Recombinant DNA Molecules:* Human H2N2, Reconstructed 1918 H1N1, and Highly Pathogenic Avian Influenza H5N1 Viruses

Presenter: Dr. Kanabrocki

Dr. Kanabrocki enumerated the tasks of the RAC Biosafety Working Group (BWG) and summarized BWG activities to date and comments from the BWG proposal presented at the September 9-10, 2008, RAC meeting. He discussed the recommendations for research with human H2N2 virus, additional guidance for H2N2 containment, and occupational health guidance for working with influenza viruses containing a a hemagglutinin (HA) gene derived from a H2N2 virus. Dr. Kanabrocki also discussed recommendations for avoiding inadvertent cross-contamination of influenza strains.

One task for the BWG is to determine Risk Group (RG) classifications for potentially pandemic influenza strains, including human H2N2, reconstructed 1918 H1N1, and highly pathogenic avian influenza (HPAI) H5N1 strains and then to determine what additional biosafety guidance, if any, should be added to the *NIH Guidelines* for research involving recombinant viruses containing sequences from these influenza viruses. The BWG considered the current guidance provided by the *Biosafety in Microbiological and Biomedical Laboratories* and the U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service, and reviewed additional scientific data.

In June 2008, a conference was convened by OBA on RG classifications and risk assessment for recombinant research with human H2N2, 1918 H1N1 influenza, and HPAI H5N1 viruses. The BWG participated in a number of teleconferences and consultations with outside experts, and an initial proposal was presented by the BWG to the RAC at its September 9-10, 2008, meeting. On December 2, 2008, a symposium, Public Health and Biosafety Practices for Research with 1918 H1N1 Influenza Virus, was held to address issues raised at the September RAC meeting, particularly the proposed use of pre-exposure prophylaxis with oseltamivir.

Dr. Kanabrocki reviewed the revisions made to the BWG recommendations based on the comments by the RAC members in September. The recommendations regarding the H2N2 virus were clarified as referring to human H2N2 viruses that circulated in 1957-1968. Human H2N2 should be classified as an RG 3 agent. The recommended containment level for research with recombinant influenza viruses containing human H2N2-specific HA from 1957 to 1968 is biosafety level 3 (BL-3) enhanced for laboratory work and BLN-3 for animal research. RG 2 recombinant influenza viruses containing H2N2 genes other than the HA gene may be conducted at BL-2 after an appropriate risk assessment. Work with the H2N2 HA gene in cold-adapted, live-attenuated vaccine strains may be conducted at BL-2 provided that the genes responsible for conferring this phenotype are not altered. He reviewed the enhancements to containment and the occupational health guidance discussed in the recommendations proposed in September. Susceptibility of the recombinant influenza viruses containing the human H2N2 HA genes to antivirals should be established either by sequence analysis to confirm susceptibility or by suitable biological assays. After genetic manipulations of genes that influence sensitivity to antivirals, susceptibility to these agents should be reconfirmed.

To avoid inadvertent recombination among HPAI H5N1 viruses, human H2N2 HA, and 1918 influenza viruses, recombinant research involving genes from these agents together or with other human influenza viruses should not be performed simultaneously within the same work area. Between experiments, good biosafety practices should be followed, including surface and biological safety cabinet decontamination according to standard BL-3 enhanced procedures; the use of separate reagents to minimize the potential for cross-contamination; and a 30-minute waiting period between experiments. Containment facilities and practices should be maintained in a manner appropriate to the highest RG virus at all times, even with lower risk group viruses when work is conducted in that same space. Manipulation of cell cultures containing the viruses should be conducted at separate times.

Individual laboratory workers should not perform concurrent influenza experiments that carry the potential risk of unintended recombination of HPAI H5N1 viruses, 1918 H1N1, and human H2N2 HA and other human influenza viruses. Between experiments, decontamination of the work area, clothing changes, and PAPR disinfection should be performed prior to handling various viruses in the same work area, and personal showers should be considered for research involving animal studies in which animal-to-animal or animal-to-human transmission might occur.

The availability of antiviral drugs as preventive and therapeutic measures is an important safeguard for research with HPAI H5N1, 1918 H1N1, and human H2N2 HA viruses. Experiments in which resistance to neuraminidase inhibitors or other effective antivirals, including investigational antivirals being developed for influenza, is deliberately transferred into these high-risk viruses would fall under *Section III-A-1 (Major Actions)* of the *NIH Guidelines* and would require RAC review and NIH Director approval. If a high-risk virus is regulated as a Select Agent, the NIH would defer action to the relevant regulatory body—either the CDC or the USDA.

The next steps for the BWG are to develop biosafety guidance for research with 1918 H1N1 viruses and HPAI H5N1 viruses taking into consideration the discussion at the previous day's safety symposium and "Points To Consider" for institutional biosafety committees on risk assessment for recombinant influenza viruses.

A. RAC Discussion

Dr. Somia summarized the issue surrounding prophylaxis that emerged from the Safety Symposium on Public Health and Biosafety Practices for Research with 1918 H1N1 Influenza Virus (cosponsored by the RAC and the Intragovernmental Select Agents and Toxins Technical Advisory Committee [ISATTAC]), which was held on December 2, 2008. At present, the practice of the Influenza Division of the CDC for working with the recombinant 1918 H1N1 influenza virus is at BL-3 enhanced, and the workers have to take antiviral pre-exposure prophylaxis. For select agent research with 1918 H1N1, the ISATTAC requires pre-exposure prophylaxis for research at BL-3 enhanced but not at BL4. The discussion at the safety symposium concerned the scientific data regarding the efficacy of prophylactic administration and use of the drug for extended periods of time. Most of the BWG members concluded that the scientific data does not support pre-exposure prophylaxis.

Dr. Federoff suggested that the BWG recommend collecting new data, despite some concern that doing so would be difficult. Dr. Roizman noted that accepting the CDC recommendations for use of prophylaxis or using BL-4 containment would significantly impact the ability of university research laboratories to conduct research in these influenza viruses, which would reduce the amount of data available for reconsideration of these proposed rules. Ms. Shapiro added that consideration should be given to the important ethical aspect about the autonomy of the researcher if prophylaxis were to be mandatory.

The CDC is not obligated to adopt the BWG/RAC/NIH recommendations. If it does not, then its current practice of requiring prophylaxis for Select Agent research will stand. Dr. Kanabrocki promised that the BWG's efforts would include all possible strategies to achieve harmonization across Federal agencies if possible.

B. Public Comment

No public comments were offered.

IV. Discussion of Human Gene Transfer Protocol #0808-946: Phase I Trial of Intratumoral Injection of Vesicular Stomatitis Virus Expressing Interferon Beta in Patients with Hepatocellular Carcinoma

Principal Investigators: Mitesh J. Borad, M.D., Mayo Clinic; Jorge Rakela, M.D., Mayo Clinic; Richard G. Vile, Ph.D., Mayo Clinic

Additional Presenters: Mark J. Federspiel, Ph.D., Mayo Clinic; Ray Myers, Ph.D., Mayo Clinic
RAC Reviewers: Drs. Bartlett, Kahn, and Roizman

Drs. Somia and Strome recused themselves from consideration and discussion of this protocol due to conflicts of interest.

A. Protocol Summary

Approximately 1 million people worldwide are diagnosed each year with hepatocellular carcinoma (HCC), and an equivalent number of patients die annually from this disease. Although the United States historically has been considered a low-incidence region, a recent increase in the incidence of HCC in this country has been observed. This increase is largely attributable to infections caused hepatitis virus type B and hepatitis virus type C (HCV). In addition to chronic liver injury and inflammation, male gender, older age, and some hereditary diseases predispose patients to HCC. Current therapies for inoperable HCC are sparse and do not significantly increase response or survival rates.

The investigators have developed a Vesicular Stomatitis Virus (VSV) as an oncolytic vector for the treatment of cancer. VSV, a Rhabdovirus, is a negative strand RNA virus, which replicates in the cytoplasm and is highly lytic, with no known transforming capabilities. VSV is arthropod-borne, and the primary hosts are rodents, cattle, horses and swine. Human infection results in very mild, flu-like illnesses, although a case of pediatric encephalitis possibly associated with VSV has been reported. Moreover, following intra-cerebral injections of macaques neuro-virulence was observed. VSV is exquisitely sensitive to the antiviral actions of alpha/beta interferons as evidenced by the finding that mice harboring a defective IFN system become highly sensitive to normally innocuous exposure to VSV. However, many tumor cells have defects in their IFN response pathways and are non-responsive to exogenous IFN. Therefore, VSV replicates to high levels in many transformed cells. In contrast, normal cells are sensitive to the anti-viral interferons produced upon infection and infection is rapidly extinguished. As a result, VSV has been shown to be a potent oncolytic agent against a variety of both human and murine tumors, of several different histological types, via intratumoral or systemic routes.

In addition, the VSV vector has been engineered to overexpress the IFN-beta (IFN-β) protein. IFN-β produced by cells that are infected with the VSV-IFN-β virus act to restrict virus replication still further in normal cells, therefore, increasing the safety of the virus; however, IFN-β produced by infected cancer cells should have little effect in blocking viral replication because the cancer cells respond very poorly to IFN-β.

The investigators have carried out studies in cultured cells in mice and in rats that indicate that VSV-IFN-β is effective at reducing the size of HCCs. In this trial, the investigators will test the safety of the VSV-IFN-β virus upon direct injection into HCCs, starting at a dose that is two orders of magnitude lower than the maximal tolerable dose (MTD) determined in the rat studies. The dose of the virus then will be escalated at levels of one-half log per level, up to a final dose of $5x10^8$ $TCID_{50}$ (50 percent tissue culture infective dose) to investigate any potential toxicities.

B. Written Reviews by RAC Members

Nine RAC members voted for in-depth review and public discussion of this protocol. Key issues included the relative novelty of the vector system that has not yet been used in clinical trials, the potential effects of a VSV overexpressing IFN-β on normal and malignant cells, and safety concerns raised by the neurotoxicity observed in a significant number of animals in preclinical studies.

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

Given that a high proportion of HCC patients are individuals who have failed earlier IFN therapy, Dr. Bartlett asked about the basis for this failure to respond to IFN in the context of chronic HCV infection and whether that failure poses a concern for HCC therapy using VSV-IFN-β. He also asked whether VSV-

IFN-β would be more likely to replicate in the liver of these individuals than in others who have not been diagnosed previously with HCV-associated cirrhosis or chronic HCV infection and treated with IFN.

Dr. Kahn limited his review of this protocol to the informed consent document. He noted several instances in which participation in this trial seemed to promise potential benefits and language (e.g., "study treatment") that overstates the potential benefits of participation. In addition, Dr. Kahn stated that two sections of the informed consent document—regarding risks of injection and injury resulting from participation—needed clarification.

Dr. Roizman requested data regarding what fraction of HCCs carry a defective IFN pathway, what happens if the virus is able to grow and produce high titers of both virus and IFN in a tumor mass lacking an operational IFN pathway, and the likely effect of a high-level release of IFN-β during the 3-day experimental period. Since the research participant is already being subjected to the trauma of injecting virus, he suggested that it might be appropriate to obtain a biopsy at that time to genotype the tumor. Dr. Roizman suggested that the investigators test artificial mixtures of wild-type and IFN-β-expressing viruses to determine at what point the wild-type virus breaks through the IFN-β-induced defense mechanisms. He also suggested that participant monitoring at 24 hours and 48 hours postinjection be made explicit and that additional information be provided about potential treatment of cytokine storm should it occur.

C. RAC Discussion

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

- Dr. Ertl asked how the investigators would deal with a delayed cytokine storm.
- Dr. Ertl suggested adding to the clinical trial followup another time point—after 8 weeks. This additional time point would assist in observing toxicity due to cytolytic T cells that can become toxic over time, especially if a virus such as HCV is also present.
- Since tumors are well vascularized, Dr. Ertl suggested intravenous (IV) administration of VSV to a few animals to understand the possibility of toxicity in humans if the vector gets into the vasculature.
- Regarding the possibility of a cytokine storm, Dr. Buchmeier asked whether development of a fever would be a sufficient signal for intervention and what other objective measures might be used.
- Dr. Federoff suggested recruiting a family member as an observer in case of a difficult-to-detect adverse event (AE).
- Dr. Buchmeier expressed discomfort with the proposed plan to send participants home who could subsequently experience a toxic reaction to overproduction of IFN-β. He requested that participants be housed either in a convalescent facility or another living situation where they would be monitored closely by the medical staff during the postdosing period, when danger would be most imminent. Particularly during the first week after dosing, it would be important to maintain close contact with the participants to check for the possibility of shock secondary to the cytokine storm.
- Dr. Roizman requested that a biopsy be included in the protocol to provide a record of tumor type in case the virus kills some tumors more aggressively than others.

D. Investigator Response

1. Written Responses to RAC Reviews

The investigators explained that it is accepted that most tumor cells *in vitro* are susceptible to VSV but that it is unknown what fraction of HCC or any tumor exhibits defects in the IFN pathway. They have initiated studies in which fresh human hepatocellular carcinomas are recovered from surgery, dissociated and then infected with VSV or VSV-IFN-β, either in the presence, or absence, of exogenously applied IFN-α or IFN-β. The replication of the virus with time will be measured, in terms both of viral proteins, infectious particles released, and cytotoxicity to the cultures. The positive (IFN-pathway intact), and negative (IFN-pathway defective), controls will be normal hepatocytes and human hepatocellular cell lines respectively that will result in data that will indicate the fraction of HCCs from patients in which viral replication is significantly reduced compared with controls by the presence of IFN, thereby providing an estimation of the number of human tumors that would be sensitive to the VSV-IFN-β strategy outlined in their proposal.

The toxicity of the VSV expressing the human IFN in the reported rat studies reflects the lack of cross-species activity of IFN-β proteins. Therefore, the toxicity observed in the Buffalo rats with the VSV-human IFN-β strongly supports the rationale for inclusion of the IFN-β gene as a safety feature in the proposed clinical trial. When the human IFN-β gene is expressed in the VSV, the investigators predict that the additional protective antiviral effect of the cytokine will protect normal human cells from VSV replication and cytotoxicity.

Preclinical experience has shown restricted viral replication through injected HCC tumors growing in mice or rats. However, if the virus does replicate well in human tumors lacking the operational IFN pathway, it would be expected to generate, concomitantly, high titers of virus and high levels of IFN-β. The locally high titers of virus released would be able to reinfect more tumor cells leading to a spreading infection, oncolysis, and destruction of tumor cells. Simultaneously, the local cytokine storm of IFN-β would be ineffective at preventing the virus from spreading within the tumor because of the defective IFN response. However, once the spreading virus reaches the edges of the tumor, and beyond (i.e. in the circulation), any normal cells that become exposed to virus as possible substrate for its replication would now be expected to posses fully intact interferon response pathways; hence, upon infection, the interferon response would shut down the cell's ability to support further virus replication rapidly and effectively. In addition, the cytokine storm formed within the tumor would likely exert highly protective antiviral effects on the normal cells outside of the boundaries of the permissive tumor.

If this trial is successful enough to result in tumor-specific, virus-spreading infection, the investigators expect to detect significant amounts of IFN-β in the circulation of participants, who will be tested for IFN-β as part of the protocol. Detectable serum levels of IFN-β would be encouraging, as it would represent high levels of viral replication in the tumor. In addition, high levels of circulating IFN-β would protect against viral infection, replication, and spread in normal, nontumor tissue, which would provide an added safety feature against systemic spread of the virus in normal tissues and organs.

In response to RAC member concerns, the investigators have initiated studies in which they will measure the levels of IFN-β locally in an injected tumor and systemically in the circulation of mice and rats, following direct intratumoral injection of VSV-IFN-β viruses. Additional animals then will be treated with tenfold to a hundredfold higher levels of recombinant IFN-β protein than those levels detected following virus treatment, and these animals will be observed for signs of toxicity, cytokine levels, and tumor growth. These studies will demonstrate whether virus replication is likely to generate sufficiently high levels of IFN-β to cause toxicities in research participants.

Preclinical data suggest that virus replicates in a tumor *in vivo* for only a few rounds of replication before it is extinguished, due to innate immune mechanisms and the difficulties of viral spread through the stroma. Therefore, the investigators believe that the virus injected into the participants' tumors will have, at most, between 3 and 5 days—approximately 10 generations—to evolve *in vivo*. Studies have shown a stable lack of mutation of VSV-IFN-β during its passage *in vitro* for the vector production process. Nonetheless, the investigators will perform sequencing studies on the virus populations as well as on individual genomes from those populations, recovered from intratumoral injections of VSV-IFN-β, to assess the percentage of clones in which critical mutations have occurred to lose IFN-β expression. They will also

undertake studies in which mixtures of wild-type VSV will be injected intratumorally, along with VSV-IFN-β. at different ratios to determine what proportion of injected viruses must be competent for IFN-β production to protect against the morbidity observed with VSV not expressing species-specific IFN-β in the Buffalo rat model.

A cytokine storm is characterized clinically by fever, myalgia, and anorexia. Participants will be monitored throughout the course of the day of administration with vital signs and also will be instructed to be in contact with the investigational team using a 24-hour contact number if clinical symptoms become develop that might be indicative of a pending cytokine reaction, so that the participant can be evaluated promptly if necessary. The treating physician will evaluate participants on days 2, 3, and 8 via history and physical exam to document changes in vital signs and symptoms; if warranted, a participant will be placed under additional direct observation. The investigators will measure serum IFN-β levels to correlate severity of symptoms with dose level along with VSV-IFN-β $TCID_{50}$ at multiple time points to ensure clearance of the virus and systemic IFN-β.

In response to the concern that normal liver cells in individuals who are HCV positive might be significantly less sensitive to the effects of IFN-β produced from the VSV-IFN-β virus, the investigators stated that it might not be clear which participants are responders as opposed to not having received optimal treatment. Those who were not optimally treated with IFN would be expected to be affected beneficially by the IFN produced from the VSV-IFN-β virus, with response against normal liver cells infected by VSV-IFN-β, HCV-infected cells, and tumor.

Normal hepatocytes next to HCV-infected hepatocytes in an individual who has failed previous IFN therapy are expected to retain their sensitivity to IFN and their protection against VSV replication and cytotoxicity. To address this issue experimentally, the investigators will attempt to infect with HCV the normal human hepatocytes already used in the preclinical studies. Such studies will approach the issue of whether prior infection with HCV is likely to make normal human hepatocytes highly sensitive to VSV replication.

All of the suggested changes to the informed consent document have been implemented, and the investigators produced a revised consent form for inclusion with their submission.

2. Responses to RAC Discussion Questions

Dr. Vile stated that the investigators are considering trying to monitor IL-8, which is closely correlated with HCV infection.

Dr. Borad explained that some HCC patients also are infected with HCV. The level of IFN response of these individuals may not be known because they received therapy for their HCV infection. Having received IFN therapy for HCV infection would be noted as part of the medical history, including whether individuals were treated, whether they had a response, and whether they had an initial response and then became resistant.

To check for toxicity if VSV is given intravenously rather than into the liver, Dr. Vile explained that the investigators had conducted studies in which VSV was administered intravenously (IV) to immunocompetent mice and that no toxicity was seen.

Dr. Borad suggested that the investigators could instruct research participants to monitor their pulses; besides fever, increased pulse is an additional objective sign of a cytokine storm. The first week after dosing is critical, and clinical and self-observation should continue for 8 weeks, after which a cytokine storm would be unlikely to occur. Dr. Vile added that, in the investigators' preclinical experience, viral replication disappears in 3 or 4 days after tumors receive an IV injection of VSV.

To address concerns about the possibility of a cytokine storm, Dr. Borad agreed to build into the protocol measurements of temperature and pulse at home as well as a detailed plan of how a toxicity event would

be handled, including how the investigators would respond to a participant's complaint of fever or changes in pulse.

The investigators agreed to implement an observational period of 1 week during which participants would be housed in a hotel near the hospital. Because clearance of the virus is seen in animals after 3 to 4 days, any cytokine problem would be unlikely in research participants beyond 1 week.

In the preclinical studies in which the investigators injected VSV into solid tumors, Dr. Vile explained that both necrosis and infiltration of immune cells are seen. Virus is detectible in the tumor only for the first few days; replication shuts down quickly.

The investigators agreed to include in the protocol a request for an optional tumor biopsy and noted that an additional biopsy might pose an additional safety concern for participants.

E. Public Comment

Dr. Borror noted wording in the informed consent document that was overly positive regarding the outcome of this study as well as the use of complex sentence structure and complicated words.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

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

Clinical/Trial Design Issues

- An efficacious response will increase viral replication and IFN production and may cause systemic IFN levels to rise, possibly triggering a cytokine storm. Although the risks of a cytokine storm and resulting serious toxicity are remote, a contingency plan should be developed. The protocol should include 24-hour, in hospital observation after administration of the vector and close clinical followup for the subsequent week. Arrangements should be made to enable participants to remain close to the hospital. Participants should be encouraged to stay with a family member or other caregiver during the 1 week after discharge from the hospital. When stable and discharged from the research unit, the participant, and their family member or other caregiver if available, should be equipped with and capable of using a thermometer, pulse monitor, and blood pressure machine, and should be instructed on when to report these readings to the clinic. The investigators should provide the participant with information about the early symptoms of IFN-β toxicity, which could include fever, increased pulse, or a significant drop in blood pressure. The PI and other clinical personnel should be accessible 24 hours a day, and participants should be provided with their contact information. The investigators were asked to submit a copy of this plan to the OBA.

- HCV infection, which is a risk factor for HCC, is often treated with IFN. There is evidence that HCV patients who develop HCC are likely to have failed IFN therapy. The cause of this failure is not clearly understood, but some data point to a complex interplay between viral and host susceptibility factors that affect the IFN response pathway. To assess effects of the IFN response pathway on VSV-IFN-β, it will be helpful to determine whether the pathway was affected by the participant's prior IFN therapy.

- Due to the potential for late-onset VSV toxicity from induced cytotoxic CD8+ cells directed against tumor cells and possibly other hepatocytes, the investigators should collect peripheral blood mononuclear cells (PBMCs) before and at a later time after vector administration (e.g., at 6 to 8 weeks); these should be cryopreserved so that they are available to elucidate unforeseen side effects that may have an immunological basis.

- The protocol should include an investigation of the relationship between the tumor's genotype and response to the vector. At the time of vector administration, the investigators should make every effort to obtain a biopsy of the participant's tumor. However, given the additional risk of biopsy, a participant's refusal to submit a biopsy should not preclude enrollment.

Ethical/Legal/Social Issues

The investigators should make the following changes to the informed consent document:

- The informed consent form states, "You will be in the study until you are no longer receiving benefit from the study agent in terms of control of the growth of your cancer." In the form, the investigators should clarify that this is a single-administration study, that in most cases discontinuation from the study indicates discontinuation of the study procedures only, and that the administration of the gene transfer product cannot be reversed.

- The document should emphasize that the study's primary goal is to establish safety and that direct benefit to the participant is highly unlikely.

- The document should include a description of the clinical monitoring that will be required after administration of the virus and the reasons for that monitoring.

- The investigators should add to the document information about the tumor biopsy and genotyping study, including the purpose and risks of the procedure.

- The investigators should remove technical terms and simplify complex words and sentences.

G. Committee Motion 2

Dr. Federoff summarized the comments and concerns of the RAC to be included in a letter to the investigators and the sponsor. It was moved that the RAC approve these summarized recommendations. The vote was 15 in favor, 0 opposed, 0 abstentions, and 2 recusals.

V. Gene Transfer Safety Assessment Board Report

RAC Reviewers: Drs. Federoff, Strome, Yankaskas, and Zaia

Dr. Zaia reported that of the 13 protocol submissions received by OBA in the past 3 months, 8 were not selected for public review at this RAC meeting. Ten protocols were for cancer, two were for infectious diseases, and one was for an eye disorder.

A total of 154 amendments were reported during this 3-month period, including 8 responses to *Appendix M-I-C-1*, two of which were discussed briefly. Protocol #0807-923, Compassionate Trial of Nanocomplex-Mediated GNE Gene Replacement in Hereditary Inclusion Body Myopathy-2, is a single-participant protocol for gene replacement for hereditary inclusion body myopathy; this protocol was reviewed at the September 9-10, 2008, RAC meeting. The amendment noted that the investigators are conducting additional studies to determine whether the glycosylation process, which is being enhanced by this experimental treatment, will produce neoantigens that might have an immune reactivity. They are also conducting additional animal studies to address this possibility. The investigators notified OBA that the single participant who was treated was without significant problems and that there was some suggestion of improvement; as a result, she will be retreated three times in the opposite extremity at 6-month intervals.

An amendment to Protocol #0807-932, A Randomized, Placebo-Controlled, Double-Blind, Dose-Escalation Study to Evaluate the Safety, Tolerability, and Pharmacodynamics of Multiple Intravenous Doses of ANZ-521 in Treatment-Naive Hepatitis C Patients, was discussed briefly; this protocol was

reviewed at the September 9-10, 2008, RAC meeting. The RAC had asked the investigators to consider the possibility that the T-cell adaptive response might lead to toxicity and to consider a longer period between dosing of participants. The investigators responded that they believe a 24-hour time interval rather than the 14 days as recommended was sufficient for various reasons; other committees and review bodies involved with this protocol have agreed with proceeding with that plan.

Dr. Zaia discussed the AEs that were reported to OBA during this reporting period. A total of 127 AEs were reported from 27 trials, of which the majority were unrelated to the gene transfer products. There were 48 initial and followup reports in which the AE was possibly related to the gene transfer products, none of which was sufficiently significant to discuss publicly at this RAC meeting.

VI. Discussion of Human Gene Transfer Protocol #0808-942: A Phase Ib, Multicenter, Single-Blinded, Placebo-Controlled, Sequential Dose-Escalation Study to Assess the Safety of Topically Applied AG013 in Subjects Receiving Induction Chemotherapy for the Treatment of Cancers of the Head and Neck

Principal Investigator:	Barbara Murphy, M.D., Vanderbilt University
Additional Presenters:	Bernard Coulie, M.D., Ph.D., ActoGeniX NV; Stephen T. Sonis, D.M.D., D.M.Sc., Brigham & Women's Hospital; Lothar Steidler, Ph.D., ActoGeniX NV
Sponsor:	ActoGeniX NV
RAC Reviewers:	Drs. Alland, Strome, and Zaia

A. Protocol Summary

Oral Mucositis (OM) is a painful, common and debilitating toxicity of many forms of drug and radiation therapy used for the treatment of cancer. Clinically, OM results in a range of mucosal damage that extends from burning erythema to opioid-requiring, full-thickness mucosal ulceration. OM is among the most frequently reported adverse events associated with cancer treatment, has a negative impact on health and economic outcomes and is estimated to affect almost 0.5 million individuals in the United States this year.

Multiple pathways contribute to mucositis development, comprising a complex series of biological events that occur within the tissues and cells of the submucosa. Despite recent advances, and although OM is frequently reported in cancer patients, treatment options are very sparse. Thus, for the majority of patients receiving cytotoxic chemotherapy and/or head and neck radiation therapy, OM represents an important, unmet clinical need.

The trefoil factor (TFF) family, which comprises TFF1, TFF2 and TFR, has been implicated in protection of the gastrointestinal (GI) tract against mucosal damage and plays an important role In its subsequent repair. All three TFF peptides have shown a therapeutic effect in experimental models and are rapidly up-regulated and secreted in an autocrine fashion In response to GI injury. Oral TFFs bind to salivary mucins and form a layer over the epithelia of the mouth, acting as a physical barrier against bacteria and noxious environmental agents. Moreover, TFF peptides have wound-healing properties and are important in protecting and healing mucosal tissues. Their potential for therapy of GI diseases as well as oral ulcers has been established.

ActoGeniX research has shown that topical application of recombinant *L. lactis* strains, engineered to secrete either human TFFI (hTFF1) or hTFF3, to the oral mucosa, favorably affected the severity and course of radiation-induced OM in an established acute radiation hamster model.

The purpose of this study is to investigate the safety, possible harms, and side effects of AG013 in participants at risk for oral mucositis (OM) and to look for clinical indication of AG013 in the reduction of the signs and symptoms of OM in individuals receiving induction chemotherapy for treatment of head and neck cancer. AG013 is made up of genetically modified *Lactococcus lactis* (*L. lactis*) bacteria that have

been modified to secrete a protein called human trefoil factor 1 (hTFF1), which is normally secreted in saliva and intestines. Human TFF1 has been shown to be important in protecting and healing mucosal tissue, such as the tissue in the mouth, when tissues are damaged by cancer therapies such as chemotherapy and radiation therapy.

The proposed Phase Ib clinical trial will enroll participants with head and neck cancer who develop OM during their first cycle of treatment with chemotherapy. OM is a painful, common toxicity resulting from the many forms of drug and radiation therapy used to treat cancer. Individuals with OM experience soreness, irritation, and ulcers in the mouth and may have difficulty eating, drinking, or swallowing as a result of their cancer treatment. During the second cycle of chemotherapy in this trial, participants will receive AG013 or placebo for 14 days at a frequency of 1 rinse, 3 rinses, or 6 rinses per day.

Throughout the study, safety will be assessed by collecting and recording AEs, conducting laboratory assessments, and monitoring the presence of *L. lactis* in blood. Vital signs—including temperature, systolic and diastolic blood pressures, heart rate, and respiration rate—will be measured and recorded at the visit before dosing and once weekly during the dosing period. A visual assessment of OM lesions using the World Health Organization scoring system will occur each day during dosing; these daily assessments will be used to evaluate the effectiveness of AG013. Information obtained from this study may improve OM care, with the final goal of the development program of AG013 being to reduce all signs and symptoms of OM.

B. Written Reviews by RAC Members

Five RAC members voted for in-depth review and public discussion of the protocol. Key issues included the use of a new transgene that might have growth effects on epithelium, the paucity of data on transgene expression *in vivo* and its biodistribution, the likelihood that the ability to make valid intergroup outcome comparisons will be limited, and the rationale for targeting a population undergoing chemotherapy induction.

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

Dr. Alland requested additional information and data regarding the culture conditions and the number of bacteria tested in studies that characterize the experimental vector as a true auxotroph *in vitro* and *in vivo*; specifically, Dr. Alland asked to see experimental evidence that *L. lactis* cannot revert at several log concentrations above those to be administered in this proposed trial. Stating his belief that the animal safety studies are inadequate because they were not matched to the anticipated human dose or to the potential participants' immune status, Dr. Alland suggested that studies be performed in profoundly neutropenic animals and that lower doses of the vector be given systemically to neutropenic animals to verify *in vivo* auxotrophy and safety.

Dr. Strome requested information about the prior use of *L. lactis* in humans and about any preclinical safety studies. He expressed some confusion about the purpose of the trial design, noting that the investigators were restricting their study to a population of patients receiving induction therapy prior to radiation and were thus excluding individuals with the most significant OM problems. In addition, because the investigators propose to include all head and neck cancer sites, differences in the primary tumors would likely obscure safety end points and the objective reporting of results. Dr. Strome noted that the entry criteria seem to suggest that participants' mouth pain would not be related to OM; using healthy controls instead of patients with head and neck cancer could reach the same safety goals.

Dr. Zaia noted that the research plan requires that participants not eat or drink 15 minutes before and 1 hour after each dosing, meaning that some participants would be without food or water for 7.5 hours each day; a contingency plan is needed for management of the emesis that will likely be induced by the chemotherapy. Dr. Zaia expressed concern that the microbiology of OM could involve coinfection with the herpes simplex virus or with commensal bacteria that could combine with the deoxyribonucleic acid (DNA) of AG013 if that DNA is not degraded sufficiently before cell lysis occurs. He noted that the informed consent document needed to include more specifics about the volume of blood to be drawn and

the purpose of the blood draw, the unlikelihood of any research participant benefiting from this study, and the importance of mentioning all potential sources of bacteremia in the risk section.

C. RAC Discussion

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

- Dr. Williams asked for clarification of the neutropenic animal (hamster) radiation model, including the level of neutropenia in that model and whether it is comparable to what is expected to be seen in the potential research participants.

- Dr. Strome suggested that, to investigate safety, the investigators should include only healthy controls, thus not running the risk of dosing an immunocompromised population. He asked the investigators to discuss their rationale for putting participants at greater risk because of their immunocompromised status, noting that the potential for efficacy would be missed but is not relevant at this Phase I level.

- Dr. Strome and Dr. Murphy disagreed about whether the induction chemotherapy proposed is currently considered standard of care.

- Dr. Strome strongly encouraged the investigators to incorporate safety data into the clinical protocol and to reevaluate carefully the study design with regard to the proposed end points.

- Dr. Federoff requested information, to be provided at a future time, about the action of bacteremia on the specific strain in the setting of an immunocompromised animal.

D. Investigator Response

1. Written Responses to RAC Reviews

The investigators reported that the available medical literature does not show any evidence that neutropenia predisposes to infection with *L. lactis*. There is no clear evidence that dairy products, and by inference *L. lactis*, are a noteworthy cause of disease, either in the healthy population or in neutropenic cancer patients with OM. The risk of infection following administration of AG013 is considered minimal, even in neutropenic cancer patients. In addition, this version of genetically modified *L. lactis*, in which the thymidylate synthetase gene has been removed completely, results in genuine thymidine auxotrophy *in vivo*.

The highest dose given in the rat and dog toxicity studies could not be increased because of physical limiting factors—the maximal amount of AG013 powder that can be suspended in a given volume and the maximal volume of buffer that can be physically and safely administered twice daily to the rat and once daily to the dog.

The sponsor has conducted pharmacokinetic (PK) experiments in the hamster OM model. These studies have shown that administration of AG013 in the cheek pouch does not lead to bacteremia or any measurable levels of hTFF1 in serum. Acknowledging that radiation-induced OM in the hamster model is not accompanied by neutropenia as seen in chemotherapy patients, the sponsor is currently conducting safety assessments of AG013 applied topically to the cheek pouch of hamsters in which concomitant OM and neutropenia (induced by myelosuppressive agents) are present. In addition, although the PK experiments in hamsters with damaged oral mucosa have shown that administration of AG013 in the cheek pouch does not lead to mucosal or systemic infection by AG013 or any measurable levels of hTFF1 in serum, these PK experiments will be repeated in the hamster safety study. To mimic the intended, clinical mode of administration, the vector will be administered as an oral rinse rather than via the systemic route.

ActoGeniX reported that it has conducted preclinical studies to support the proposed clinical trial, including 14-day good laboratory practices (GLP) toxicity studies with AG013 in two relevant animal species—rat and dog, both of which are hTFF1 cross-reactive. No treatment-related abnormalities were noted in these two toxicity studies, in which the animals were dosed by an intragastric oral gavage of AG013. In addition, the sponsor is currently conducting safety assessments of AG013 applied topically to the cheek pouch of hamsters, in which concomitant OM and neutropenia are present.

Regarding other clinical studies, ActoGeniX noted that a comparable engineered *L. lactis* strain that secretes the anti-inflammatory and immunomodulatory cytokine human IL-10 has been administered daily for 1 week to Crohn's disease (CD) patients. This product was assessed for safety and tolerability in a Phase I study in 10 participants with moderate to severe CD; it was formulated to result in release in the distal small intestine. The CD participants had a non-intact mucosal layer in the ileum and colon, and despite being treated with concomitant immunosuppressive therapy, the product showed good tolerability, safety, and environmental containment without evidence of bacteremia.

The investigators explained that the primary objective of this Phase Ib protocol is to evaluate the safety and tolerability of three total daily dose levels vs. matching placebo, using different dosing frequencies, of AG013 applied topically to the oral mucosa. The possible effect on the extent and severity of OM is solely an exploratory end point. As such, the current Phase Ib protocol has the appropriate dosing regimen for investigating safety.

Through a literature search that did not uncover any effects and because AG013 will be administered for 14 days, whereas the chemotherapeutic agents will be given for only 3 or 4 days, ActoGeniX believes that cisplatin, fluorouracil, and docetaxel will not alter the desired effect of the *L. lactis* production of hTTF1.

Experiments in the hamster model of OM combined with a literature search have led to the conclusion that, in the unlikely event of bacteremia, research participants' levels of serum thymidine will not be sufficient to provide a permanent source of thymidine to rescue the bacteria.

Because nausea and vomiting are a concern in this patient population, the protocol will include the availability of antiemetic treatment.

ActoGeniX agreed to incorporate all of the suggested changes into the informed consent document.

2. Responses to RAC Discussion Questions

Dr. Murphy explained the investigators' choice of participant population. They do not want to test this new drug in individuals who have the worst OM. Participants who are at risk for OM or for whom OM will be self-limited constitute the most appropriate population. Using a healthy control population to make sure that there is no evidence of blood cultures positive for the bacteria is possible, but the investigators want to garner at least some efficacy data, in part because a Phase I trial in CD patients indicated some efficacy, with 8 out of 10 participants in that Phase I study reporting clinical benefit. A high-risk OM participant population can help answer some of the questions of safety in the patients who would eventually receive this drug and could help indicate efficacy.

Dr. Sonis stated his belief that the investigators' ability to glean useful safety information from this trial would be undermined if they did not study this investigational drug in the patient population at risk for OM. He added that OM in the head and neck cancer population represents only 15 percent of those cancer patients who get OM; the larger OM population consists of patients with solid tumors such as breast, colorectal, and lung cancers. The investigators are trying to uncover safety information in as broad a group as possible to be applicable across the broadest range of cancer patients at risk for OM.

Dr. Coulie noted that the investigators have conducted Phase I and ongoing Phase II clinical studies in immune-compromised patients with non-intact mucosa that have shown no evidence of bacteremia or sepsis. However, he acknowledged that CD patients and neutropenic patients are both immunocompromised in very different ways.

E. Public Comment

No public comments were offered.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

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

Preclinical Issues

- The *L. lactis* strain (sAGX0085) has been modified for safety reasons to make it incapable of surviving in a thymidine-deficient environment. However, the vector cannot be contained if the modification is reversed through recombination or by other mechanisms. Although the reversal effect has not been seen in preclinical experiments, the stability of the modification should be established further through *in vitro* experiments with sAGX0085 at concentrations that are several logs above those to be administered in the protocol.

- The chemotherapy that the participants receive as part of their cancer treatment is likely to result in neutropenia, which will increase their risk of infection. Although *L. lactis* is thought to be safe in normal individuals, in isolated cases, it has caused clinical disease. And although the protocol involves local, not systemic, administration, it is possible that some bacteria will be absorbed systemically. To further define the risk, the investigators should conduct additional studies of low-dose systemic administration in a neutropenic animal model. In addition, the investigators should confirm that the level of white blood cells in the neutropenic hamster model corresponds to clinical neutropenia.

Clinical/Trial Design Issues

- The study proposes to use head and neck cancer patients who are to receive docetaxel plus cisplatin and fluorouracil (TPF) induction chemotherapy, but there is still a lack of consensus as to whether this is the standard of care for these patients. The protocol should acknowledge that TPF induction therapy is not uniformly accepted as the standard of care for head and neck cancer and should explain why the patients undergoing this chemotherapy have been selected for the study. A related point is that the protocol should include a discussion of why cancer patients receiving chemoradiation, who have a greater risk of OM and are likely to be a population that would most benefit if the intervention proved efficacious, were not chosen to participate in this initial safety study.

- Although the goal of this study is to assess safety, one rationale for enrolling individuals with head and neck cancer, rather than healthy volunteers, is to evaluate the secondary end points of efficacy. However, it is highly unlikely in this small number of participants with a diversity of tumor types that the current study design will be able to measure the efficacy end points in a statistically relevant manner. As such, the protocol should justify the selection of the study population and explain why the design does not involve a more homogeneous group of head and neck cancer patients.

Ethical/Legal/Social Issues

- The investigators should address the inconsistency that appears in the informed consent document section "What Other Treatments Are Available." The statement that there are no alternative treatments is contradicted later in the section when reference is made to alternative treatments.

G. Committee Motion 3

Dr. Federoff summarized the comments and concerns of the RAC to be included in a letter to the investigators and the sponsor. It was moved that the RAC approve these summarized recommendations. The vote was 17 in favor, 0 opposed, 0 abstentions, and 0 recusals.

VII. Discussion of Human Gene Transfer Protocol #0808-934: A Phase I, Open-Label Study of the Safety, Tolerability, and Therapeutic Activity of JVRS-100 Cationic Lipid-DNA Complex in Patients with Chronic Hepatitis C Infection Who Relapsed After Receiving Interferon-Ribavirin Treatment

Principal Investigator:	John McHutchison, M.D., Duke University Medical Center
Other Presenters:	Thomas Monath, M.D., Juvaris BioTherapeutics, Inc.; John Warner Ph.D., Juvaris BioTherapeutics, Inc.
Sponsor:	Juvaris BioTherapeutics, Inc.
RAC Reviewers:	Drs. Ertl and Kirchhoff and Ms. Shapiro

AND

Discussion of Human Gene Transfer Protocol #0808-936: A Phase I Trial of the Immunostimulant JVRS-100 for the Treatment of Patients with Relapsed or Refractory Leukemia

Principal Investigator:	David F. Claxton, M.D., Penn State Hershey Cancer Institute
Other Presenters:	Thomas Monath, M.D., Juvaris BioTherapeutics, Inc.; John Warner Ph.D., Juvaris BioTherapeutics, Inc.
Sponsor:	Juvaris BioTherapeutics, Inc.
RAC Reviewers:	Dr. Ertl, Ms. Shapiro, and Dr. Williams

Dr. Federoff explained that JVRS-100, proposed for use in both protocols, is a cationic liposome-non-coding plasmid DNA complex. Because both protocols propose to use the same experimental complex, the RAC reviewed the proposals together.

A. Summary of Protocol #0808-934

JVRS-100 utilizes cationic liposome and plasmid DNA complexes that interact with toll-like receptor (TLR) pathways, and possibly other cytosolic DNA sensor-activation pathways to activate the innate immune response and, when combined with disease-specific antigens, the adaptive immune response. No foreign genes are encoded in the plasmid DNA for expression in human cells. When tested as separate components, the liposome and DNA exhibit negligible or low-level immune induction, respectively; however, when combined, the liposome-DNA complexes induce substantial T_H1 cytokine levels and natural killer (NK) cell activity. The liposome component protects the DNA from extracellular degradation, and enhances uptake of the particulate complexes by cells into the TLR-rich endosomal compartment of dendritic cells and macrophages. As a result, JVRS-100 induces T_H1 cytokine responses, including interleukin-12 (IL-12), interferon-gamma (IFN-γ) and interferon-alpha/beta (IFN-α/β) as well as NK cell activity. These cytokines have antiviral and anti-tumor activities.

Due to their ability to induce interferons, JVRS-100 is being developed by Juvaris BioTherapeutics, Inc. (Juvaris) for the treatment of patients with chronic hepatitis C refractory/relapsed to standard therapy (peginterferon and ribavirin). The initial proposed study is a Phase I, open-label, dose-escalation study of JVRS-100 to evaluate the safety and tolerability of JVRS-100 and to evaluate the ability of JVRS-100 to reduce HCV viral load. This study will first determine the safety and tolerability of a single administration of ascending doses of study medication. Once a maximum tolerated dose (MTD) is determined, participants will enter the Repeat-Dose Phase of the study, wherein the safety, tolerability and antiviral activity of three sequential intravenous treatments at the MTD (administered at 10-day intervals) of JVRS-

100 will be determined. Subsequent studies will address the safety and efficacy of JVRS-100 for the treatment of participants who do not respond to standard treatment (non-responder population) and patients who are treatment naïve. It is anticipated that, ultimately, JVRS-100 will be investigated as part of a combination therapy with small-molecule antiviral drugs, including ribavirin.

B. Written Reviews of Protocol #0808-934 by RAC Members

Seven RAC members voted for in-depth review and public discussion of the protocol. Key issues included potential safety issues raised by this novel approach, concerns about potential unanticipated side effects, and known toxicities seen with IV administration of liposomal complexes.

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

Dr. Ertl suggested that the informed consent document contain explicit information about standard treatment options available to potential research participants and noted that participation in this trial could reduce as well as increase the efficacy of that treatment. She suggested expanding the timing for dose escalation to 3 weeks, citing the investigators' expectation that CD8+ T cells might reduce viral burden by lysing infected hepatocytes, which could result in the potential of liver toxicity. Dr. Ertl suggested that participants who experience a grade 3 or grade 4 serious adverse event (SAE) should be excluded from further dosing, instead of the proposed reduction in dose. With regard to the specifics of this protocol, she suggested that cytokines be tested more often and that T-cell studies be conducted more frequently using an intracellular cytokine staining assay that distinguishes between CD4 and CD8 responses rather than the enzyme immunospot assay. Dr. Ertl also suggested that kinetics studies for T cells should be conducted, because immunomodulation might cause T-cell expansion, whereas reduction of antigen might cause T-cell contraction.

Dr. Kirchhoff noted the critical issue of choice of doses of JVRS-100 to be administered to participants, also observing that JVRS-100 does not encode an immunostimulatory protein. Although the benchmark for assessing the side effects of treatments for HCV infection is the constellation of side effects caused by one component of the standard treatment for HCV (pegylated IFN), he noted that the combination of CpG motifs and cationic liposome, both of which are immunostimulants, is fraught with substantial risk of serious side effects. Dr. Kirchhoff suggested updating information about immune stimulation by CpG motifs for controlling chronic HCV infection, an essential element in the desire to test JVRS-100.

Ms. Shapiro suggested that disclosure of appropriate alternative procedures or courses of treatment that might be advantageous to potential participants should be disclosed in the informed consent document and that a discussion should be included about the financial relationship between the sponsor and the PI. The risk section should include a discussion of the possibility that participants who receive the investigational drug might experience reduced efficacy of subsequent standard treatment. She noted the need for greater clarity throughout the informed consent document regarding the costs of research-related injuries and in the section about withdrawal of consent for research use of biospecimens.

C. Summary of Protocol #0808-936

Juvaris has developed a novel drug called JVRS-100, composed of complexes of cationic lipid and DNA that strongly increase immune responses. Cationic lipids are positively charged molecules that bind to negatively charged DNA, forming a complex the size of a large virus and facilitating entry into cells involved in the immune response. The DNA in this complex is derived from *E. coli*; it does not contain any foreign genes. Instead, the DNA is recognized as a "danger signal" by the cell, similar to the signal that would occur when bacteria invade the body. In response, cells produce cytokines such as IFN-α, IFN-γ, and IL-12 and stimulate NK cells. These cytokines and NK cells constitute the innate immune system, a nonspecific form of immunity designed to rid the body of infections caused by microorganisms. In addition, when the nonspecific innate immune response is activated, the body also responds by making antibodies and T cells to combat the invading microorganism. JVRS-100 can be used to harness the body's innate and adaptive immune systems to treat patients with cancer.

The initial proposed clinical study will evaluate both the safety of JVRS-100 and the ability of the immune response stimulated by the drug to remain under standard physiological control mechanisms. The research participants to be dosed with JVRS-100 will be males and females, at least 18 years old, with relapsed/refractory leukemia (first or subsequent relapse).

The study will proceed in two stages to minimize the number of participants treated at doses substantially below the recommended Phase II dose. In stage 1, an accelerated titration schema will be followed, with one participant at each dose level. Stage 2 will have three to six participants at each dose level until a recommended Phase II dose is determined. The cohort then will be expanded to a maximum of 12 participants to more fully evaluate the recommended Phase II dose. Follow-on studies will address the efficacy of JVRS-100 for treating patients with relapsed/refractory acute leukemia. Assuming a successful outcome to the proposed study, subsequent studies may include research participants with myelodysplastic disorders and acute leukemia following presentation, given in conjunction with chemotherapy. Expansion of the experimental treatment into other hematopoietic and solid-tumor types also would be considered based on medical need and probability of success.

D. Written Reviews of Protocol #0808-936 by RAC Members

Seven RAC members voted for in-depth review and public discussion of the protocol. Key issues included potential safety issues raised by this novel approach, which involves deliberate induction of an innate immune response, concerns about potential unanticipated side effects such as a cytokine storm, and known toxicities seen with IV administration of liposomal complexes that potentially could be augmented in the setting of induction of cytokines.

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

Dr. Ertl stated that the preclinical efficacy data are unimpressive and suggest that, in a transplantable tumor model, increased survival is linked to CD8+ T cells, which are often functionally impaired in progressing cancers. She noted that a dose-escalation safety study with an N of 1 (such as this proposed study) and the study stopping criteria were both unacceptable. Dr. Ertl suggested that the investigators test the participants' sera for IL-6 and explain their rationale for specific markers for testing. She also asked the investigators to request permission for autopsy in case of study-related death and asked why the investigators stated that injury resulting from this research would not be treated free of charge.

Ms. Shapiro asked the investigators to clarify the description of the side effects in humans of JVRS-100 and to eliminate or reword a sentence in the informed consent document that could result in therapeutic misconception. She noted as problematic the statement that participants would be responsible for all treatment costs for research-related injuries, especially in light of the provision of no-cost treatment for research-related injuries in the HCV protocol.

Dr. Williams asked about the total number of animals tested with the empty vector for toxicity analysis. Since animal studies with JVRS-100 demonstrated thrombocytopenia and elevated cholesterol, he asked the investigators to comment on these assays and any evidence of disseminated intravascular coagulation. The toxicity study in cynomolgus monkeys included preadministration of aspirin, but the clinical trial does not propose to do so; Dr. Williams requested that the investigators explain their reasoning. He also asked for an explanation of the schedule and dosage for the proposed trial as well as the markedly lower dose in the proposed clinical trial compared with the dosage in the monkey study. Dr. Williams requested that the investigators discuss how the entry criteria of 3 months posttransplantion was arrived at, given that full immunological reconstitution following stem-cell transplantation is usually delayed, sometimes for many months.

E. RAC Discussion of Protocols #0808-934 and #0808-936

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

- For Protocol #0808-934, Dr. Zaia asked how the investigators would define a dose-limiting toxicity and suggested a thorough consideration of that definition.

- Noting that the innate immune response is extremely variable, Dr. Ertl explained that the RAC is always concerned about inducing innate immunity; a cytokine inducer, as in this proposed trial, that causes minimal toxicity in animals could cause death in humans. Innate immunity is individualized and influenced by underlying genetic conditions, diseases, and potential coinfections. Therefore, proposing an N of only 1 in Protocol #0808-936 is not advisable.

- For Protocol #0808-936, Dr. Alland discussed concerns about the risks to participants when exclusion criteria are not strictly delineated, especially when a participant is likely to die if he or she does not get some sort of therapy. He suggested implementing strict inclusion criteria that would state that participants could enroll who "have no alternative" as opposed to those who are "unlikely to have an alternative." Doing so would ensure that objective enrollment criteria are applied potential participants who might have an alternative therapy.

- Since the investigators are targeting elderly patients for inclusion in Protocol #0808-936 and because recovery among that age group can be slow, Dr. Ertl suggested that the investigators test potential participants for CD8 T cells before entering them into this trial.

F. Investigator Responses

1. Written Responses to RAC Reviews of Protocols #0808-934 and #0808-936

Preclinical toxicology studies with JVRS-100 as well as a pilot study in HCV-infected chimpanzees indicated that cytokine responses were limited in magnitude and duration, returning to baseline within 24 hours, and that all treatments were well tolerated.

Based on the likely mechanism of action of JVRS-100, which involves induction of IFN and other cytokines, the investigators believe it is unlikely that this experimental treatment would induce resistance to retreatment, just as IFN treatment has not been associated with resistance to subsequent IFN treatments.

During the stage 1, single-dose portion of the proposed clinical trial, participants will be monitored on an inpatient basis, and samples for cytokine testing will be collected prior to dosing as well as five times within the initial 48 hours after dosing. Given the inpatient nature of this portion of the study, the cytokine profiling and safety monitoring in effect during that period, and the cytokine profile data from nonhuman primate studies, the investigators believe that the addition of new research participants to a dosing cohort 48 hours (instead of 24 hours) following the last participant's dosing is safe and reasonable.

HCV-infected chimpanzees treated with 25.8 μg/kg, which is significantly higher than the dose proposed for the human clinical trial, resulted in limited and transient activation of systemic cytokines. In particular, IFN-α and IL-6, and to a lesser extent IFN-γ, IL-12, and TNF-α, cytokines were increased transiently in chronically HCV-infected chimpanzees, with return to baseline within 24 hours.

The investigators explained that the central rationale for evaluating JVRS-100 therapy for individuals chronically infected with HCV is based on the ability of JVRS-100 to effectively induce innate immune responses in different animal models, including chimpanzees. These immune responses are known correlates involved in the control and/or reduction of HCV infection. Although the JVRS-100 data in chimpanzees are promising, the investigators noted that they are limited in scope due to the nature of the model; therefore, a human trial is warranted to determine the antiviral activity of JVRS-100.

Hypothetically, there is potential for T-cell induction in research participants dosed with JVRS-100, although this is not the primary focus of the proposed study. However, the investigators presume that in the context of innate immune activation by JVRS-100 and the potential presence of existing HCV

antigens in the participant, ancillary T-cell activation might occur. In studies to determine whether JVRS-100 is capable of activating a cellular immune response, PBMCs from patients with chronic genotype 1 HCV infection were stimulated *in vitro* with JVRS-100 mixed with recombinant HCV core or nonstructural protein antigens. PBMCs from these individuals showed activation when exposed to JVTS-100 alone or with various HCV proteins. The investigators will perform T-cell studies in research participants if an antiviral effect is seen.

The stopping rule for the study is the occurrence of any serious or grade 4 AE or any unexpected grade 3 AE. Expected grade 3 AEs are those associated with IFN-like symptoms (e.g., fever, headache, myalgia). If expected, severe grade 3 signs and symptoms or abnormal clinical laboratory events occur that do not constitute study-stopping AEs in participants in the repeat-dose phase of this study and if those AEs are not serious enough to stop the study, dose adjustment will be performed according to a specified algorithm.

The toxicology protocol using aspirin was reviewed by FDA in support of an earlier Valentis trial. The exact rationale for aspirin treatment is not documented in available records, but it is possible that it was done to challenge or exacerbate any potential pathologic consequences of drug-induced thrombocytopenia or platelet dysfunction.

2. Responses to RAC Discussion Questions of Protocol #0808-936

Dr. Claxton agreed that a grade 4 toxicity event that is related to the experimental treatment would trigger a stopping of the trial until the appropriate reviews are conducted. He explained that the investigators will test for antitumor cytotoxicity and NK-cell activity and, where encountered, will study it in greater detail.

In response to concerns about enrollment conflicts of interest, Dr. Claxton agreed to implement strict inclusion criteria and to have a colleague review questionable cases to ensure that enrollment is appropriate for each potential participant.

The investigators agreed to incorporate all of the suggested changes to the informed consent document as well as to rewording the inclusion/exclusion criteria to clarify which patients would be excluded from participation in this protocol.

G. Public Comment on Protocols #0808-934 and #0808-936

No public comments were offered.

H. Synopsis of RAC Discussion and RAC Observations and Recommendations

1. Protocol #0808-934

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

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

- JVRS-100 may lead to T-cell expansion due to its immunomodulatory activities or to T-cell contraction due to loss of HCV-infected hepatocytes and therefore reduction in viral antigens. To understand better the effect of this proposed therapy on cellular immune response, PBMCs should be collected at one early time point after dosing (e.g., day 7) and at a later time point (e.g., day 30).

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

- Patients with HCV infection who initially do not respond to IFN therapy still have as much as a 30-percent chance of achieving sustained virologic response with retreatment. This option

should be discussed in the informed consent document, and the fact that clinical benefit is not expected from participation in this study should be acknowledged. Potential participants should be informed that failure to respond to IFN therapy in the past could indicate that the participant is less likely to receive any clinical benefit from JVRS-100. In addition, the possibility should be acknowledged that receiving JVRS-100 might reduce the chance of responding to retreatment with IFN therapy in the future.

2. Protocol #0808-936

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

Clinical/Trial Design Issues

- The population of "relapsed and refractory" leukemia patients is not homogeneous. Since some patients are much more likely to respond to salvage chemotherapy for acute lymphocytic leukemia and acute myelogenous leukemia than others, the inclusion and exclusion criteria should be refined so that individuals who are unlikely to respond or be able to tolerate chemotherapy (e.g., advanced age may be a determining factor) are included, and those who may do well on chemotherapy are excluded from the study. More complete and specific inclusion/exclusion criteria serve to limit the investigator's discretion in the selection of participants, which is particularly appropriate in this situation because the investigator is also a clinician and will be in a position to recruit his own patients.

- The proposed dose-escalation plan of one participant per cohort may be more appropriate to chemotherapy studies in which the experimental drug's dose/response/toxicity curves are more predictable. Since immune responses to immune-based therapy are more variable, toxicities may not be detected in a single participant. A dose-escalation design of three participants per dose cohort would be more appropriate.

- The protocol requires that if two or more participants experience the same grade 2 or higher AE, enrollment would be halted temporarily until the data and safety monitoring board (DSMB) reviews the data and allows the enrollment of additional participants to proceed. This refers to participants treated at any dose, including across cohorts. Certain toxicities can be expected in immunotherapies. Therefore, it might be advisable to tailor the type of grade 2 toxicities that would lead to a temporary suspension of the trial.

- A stopping rule should be established for any grade 4 toxicity that can be reasonably associated with the experimental intervention.

- Preclinical data indicate that the efficacy of this immunotherapy may rely on adaptive and innate responses. In those participants who have undergone bone marrow transplant (BMT) within the prior 6 months, immune reconstitution should be documented by measurement of CD8+ cells prior to dosing.

Ethical/Legal/Social Issues

- The statement, "Because it is experimental, the therapy offered in this research is only available to you if you take part in the research study" should be deleted from the informed consent document. The intervention should not be misconstrued as therapy.

I. Committee Motion 4

Dr. Federoff summarized the comments and concerns of the RAC to be included in a letter to the investigators and the sponsor. It was moved that the RAC approve these summarized recommendations. The vote was 15 in favor, 0 opposed, 0 abstentions, and 0 recusals.

VIII. Day 1 Adjournment

Dr. Federoff adjourned Day 1 of the December 2008 RAC meeting at 4:45 p.m. on December 3, 2008.

IX. Day 2 Call to Order and Opening Remarks

Dr. Federoff, RAC Chair, opened Day 2 of the December 2008 RAC meeting at 8:00 a.m. on December 4, 2008.

X. Update on Allogeneic Bone Marrow Transplantation for X-SCID

Presenters: Rebecca H. Buckley, M.D., Duke University Medical Center (DUMC); Morton J. Cowan, M.D., University of California, San Francisco (UCSF) Children's Hospital; and Richard J. O'Reilly, M.D., Memorial Sloan-Kettering Cancer Center

A. Introduction

The RAC had previously reviewed the clinical and molecular data concerning five AEs that occurred in two human gene transfer studies being conducted in France and England to correct X-SCID. The studies involved engraftment of an autologous bone marrow-derived, CD34+ hematopoietic stem-cell enriched cell population transduced with a Moloney murine leukemia retrovirus-derived replication incompetent vector encoding the common gamma chain (γc) transmembrane protein subunit shared by receptors for Interleukins 2, 4, 7, 9, 15, and 21. The children in the studies developed T-cell acute lymphoblastic leukemia almost 3 years or more after receiving the gene transfer. The leukemias appear to share the common causative mechanism of insertional mutagenesis at or near oncogenes, which contributed to the abnormal growth of these leukemic cells

B. Presentations

Dr. Cowan provided an overview of hematopoietic cell transplantation (HCT) for SCID to replace defective lymphocytes with normal ones donated by a matched sibling or unrelated donor, or haploidentical parental donor from bone marrow, peripheral blood, or umbilical cord blood. Immunosuppressive or ablative treatments may be used to prevent rejection or make space to give a selective advantage to the donor cells. He defined a cure as durable engraftment of donor cells, clearing of viral infection and reconstitution of T cells. X-SCID, the most common form of SCID accounting for 40-50% of cases, is often not diagnosed, despite the existence of diagnostic tools allowing for newborn screening, until the babies present with infections. He reviewed the types of allogeneic donors for X-SCID: HLA-matched siblings, matched unrelated adult volunteer donors (MUD), unrelated umbilical cord blood donors (UCB), and haplocompatible relatives and the recent experience with HCT for X-SCID at UCSF Children's Hospital. He talked about the risks of HCT with alternative donors including the time to find a donor, graft vs. host disease (GVHD), organ toxicity with conditioning, and quality and durability of T cell engraftment and the contraindications to HCT for X-SCID.

Dr. Buckley provided an update on BMT for X-SCID at Duke. She provided background on SCID as a fatal syndrome of diverse genetic origin characterized by the absence of T- and B-cell (and sometimes NK-cell) functions. Twelve genes have been identified including γc involved in XSCID. Out of the 200 SCID patients seen by Dr. Buckley over many years, 90 of them (45 percent) were X-SCID patients.

Bone marrow transplantation for SCID was first used successfully in 1968. Until 27 years ago, this required strict HLA identity between donor and recipient to avoid lethal GVHD. This can be avoided by T cell depletion of the donor marrow, which allows use of half-matched parental donors and the omission of immunosuppressive GVHD prophylactic drugs. She reviewed experience with HCT for SCID at Duke between 1982 and 2008, including the causes of death in 37 SCID patients after BMT mostly from infection. She also discussed chimerism and B-cell function after BMT and the clinical features of SCID patients long term and clinical status post-BMT.

Dr. Buckley concluded that SCID is a pediatric emergency, and the potential exists to diagnose this condition routinely at birth. If a rigorously T-cell-depleted, stem-cell transplant from a relative can be performed in the first 3.5 months of life without pretransplant chemotherapy or posttransplant GVHD prophylaxis and before infections develop, the probability of success is 94 percent. T-cell-depleted haploidentical BMT provides lifesaving therapy for all forms of SCID, but it is not a perfect treatment.

Dr. O'Reilly discussed the long-term results of T-cell-depleted HLA haploidentical marrow allografts administered with or without myeloablation. HLA-haplotype-disparate, T-cell-depleted hematopoietic progenitor grafts can provide durable reconstitution of immunity in patients with SCID. Engraftment and T-cell reconstitution are impaired in SCID patients with NK function or adenosine deaminase (ADA) deficiency unless preparatory myeloablation is employed. Without myeloablation, engraftment of donor B cells and NK cells is rare, leading to sustained deficiency of humoral immunity and NK-cell functions. Without myeloablation, engraftment may provide full reconstitution of T-cell immunity. However, thymic output and T-cell activity decline in a percentage of patients who are 15 to 20 years post-transplantation, which may predispose these patients to chronic infection and autoimmune disorders. SCID patients prepared with myeloablation have consistently achieved full reconstitution, mediated by donor T, B, and NK cells, which has been sustained through 15 to 24 years of followup. Novel, less toxic approaches are being evaluated for preparatory myeloablation and for the use of secondary grafts administered before adolescence to reconstitute populations of B and NK cells in T-cell chimeras. Issues surrounding the limitations to B-cell depletion long term, including the cost of intravenous immunoglobulin (IVIG), will be critical in evaluating new approaches to treating X-SCID.

C. RAC Discussion

Dr. Strome asked about the problem with B cell engraftment. Dr. Buckley responded that in X-SCID, the B cells are phenotypically normal but do not function to class switch due to six abnormal cytokine receptors on the cell surface. The use of rituxan has been proposed to eliminate the non-functional B cells to allow better B cell engraftment.

Regarding the possibility of mass screening of newborns, Dr. Cowan noted that mass screening is being tested in Wisconsin by measuring small DNA fragments called T-cell receptor excision circles (TRECs), which are byproducts of the production of normally functioning T cells and which are detectable in whole blood. A SCID baby does not produce normal T cells and thus does not develop an immune system and will not have detectable TRECs. To date, the State of Wisconsin has screened approximately 50,000 babies. Even though Wisconsin officials have not yet identified a SCID child, which is to be expected statistically, they have identified two DiGeorge syndrome children and one neutropenic child, all of whom were transplanted successfully. A screening trial will begin within the next 6 months on a Navajo Reservation where the incidence of SCID is higher; the same TREC approach will be used. A number of other States are in the process of evaluating whether to require newborn screening to detect SCID.

Dr. Federoff asked the presenters how they would discuss with potential participants whether they should enroll in an X-SCID gene transfer protocol. Dr. Buckley said she would recommend transplantation but that she hoped that gene therapy, once perfected, would be a future option. Dr. Cowan stated that there is no contraindication for transplantation but that there is a great potential for gene therapy as a durable long-term cure. In advising his patients' parents, he would make sure that the child's immune reconstitution is good, that the delay of failure to reconstitute immunity would be minimal, and that the risk of leukemia, which is currently at 25 percent, is low. Dr. O'Reilly stated that transplantation is the first

option for the patient who is relatively healthy, could be transplanted in an outpatient setting, and is very young and therefore would not experience the issues of later-in-life transplantation. However, he also noted that performing a transplant to stabilize a patient and then administering gene therapy is an attractive treatment plan. Dr. O'Reilly stated that such "secondary" gene therapy should be administered soon after stabilization of the patient, because of the concern that the microenvironment essential to early development of the precursors might disappear quickly in the course of normal development. He added that evidence of this concern is the lack of success in early gene transfer trials in which an older patient receives genetically modified cells; in these cases, the outcome is significantly different compared with administering gene transfer to younger children.

Dr. Strome asked whether the primary potential benefit of gene transfer is to eliminate the need for IVIG. Dr. Buckley responded that the need for IVIG is a major concern, but the other concern is head-to-toe warts that are difficult to control, especially noted in the most NK-deficient patients. Dr. O'Reilly responded that patients who are meticulous about IVIG replacement do extremely well, but other non-medical circumstances sometimes result in a treatment lapse, and they then develop chronic lung disease. In the absence of an effective B-cell system and in the absence of an effective NK-cell system, in the long term these patients are prone to cell-mediated autoaggressive responses such as chronic active hepatitis. Dr. Cowan explained that a fully matched transplant is the best situation, so the goal is to correct and restore the patient's own T-cell, B-cell, and NK-cell numbers and functions.

Dr. Takefman asked about the key factors in determining the appropriate age for transplant. Dr. Buckley explained that it appears that transplantation by 3.5 months may be best, possibly because the thymus is better able to educate the stem cells at that age or because viral infections may have a profound effect on thymic function. Dr. O'Reilly added that viral infections are markedly higher in patients who are between 3 and 6 months old, which means that many of these patients are very sick when they arrive for treatment; in addition, antivirals (e.g., ganciclovir) can be immunosuppressive.

D. Public Comment

Dr. Brian Sorrentino, St. Jude Children's Research Hospital, asked how much busulfan would be necessary to enact the optimal increase in B-cell and NK-cell engraftment using subablative conditioning with busulfan, which is an approach that has proven important in gene transfer with ADA-SCID. Dr. O'Reilly responded that this worthwhile question needs to be addressed, but doing so is difficult because of the rarity of X-SCID. Dr. Cowan responded that low-dose or half-dose busulfan is a question that needs to be addressed; however, gene therapy protocols should concentrate on approaches that do not rely on any conditioning. In addition, he noted that 95 percent of the busulfan crosses the blood-brain barrier, so busulfan gets into the brains of these young children.

XI. Discussion of Human Gene Transfer Protocol #0808-950: Gene Therapy for X1-SCID Using a Self-Inactivating (SIN) Gamma-retroviral Vector

Principal Investigators:	Luigi D. Notarangelo, M.D., Children's Hospital Boston, and Adrian Thrasher, M.D., Institute of Child Health, London, England
Additional Presenter:	Christopher Baum, M.D., Hannover Medical School, Hannover, Germany, and Cincinnati Children's Hospital Medical Center; Donald Kohn, University of Southern California,
Sponsor:	David A. Williams, M.D., Children's Hospital Boston/Harvard Medical School
RAC Reviewers:	Drs. Fan, Federoff, and Kodish
Ad hoc Reviewer:	Naomi Rosenberg, Ph.D., Tufts University

Drs. Wei and Williams recused themselves from consideration and discussion of this protocol due to conflicts of interest.

A. Protocol Summary

Severe combined immunodeficiencies (SCID) are a heterogeneous group of inherited disorders characterized by a profound reduction or absence of T lymphocyte function. They arise from a variety of molecular defects which affect lymphocyte development and function. The most common form of SCID is an X linked form (SCID-X1) which accounts for 40-50% of all cases. SCID-X1 is caused by defects in the common cytokine receptor γ chain (γc), which was originally identified as a component of the high affinity interleukin-2 receptor (IL-2RG), but is now known to be an essential component of the IL-4, -7, -9 -15, and -21 cytokine receptor complexes. Classic SCID-X1 has an extremely poor prognosis without treatment. Death usually occurs in the first year of life from infectious complications unless definitive treatment can be administered. Until the recent advent of somatic gene therapy, hematopoietic stem cell transplantation (HSCT) offered the only curative option for patients with any form of SCID. If a genotypically matched sibling donor is available, HSCT is a highly successful procedure. However a genotypically matched family donor is only available for approximately 30% of patients. For the remaining individuals, alternative donor transplants, principally from matched unrelated (MUD) or haploidentical parental donors have been performed. In these situations, 20 percent to 30 percent of patients will not survive. When a parent is the donor, about half of patients who do survive are not fully cured because the T lymphocytes are replaced, but the B lymphocytes still do not work. When an unrelated person is the donor, the patient typically gets high-dose chemotherapy, which kills off the patient's bone marrow and allows full replacement of T cells and B cells, but these patients often have long-term problems resulting from the chemotherapy. BMTs from both parents and especially those from unrelated people can cause GVHD, a condition in which donor lymphocytes in the BMT recognize the patient's own organs, such as skin and gut, as foreign and cause severe damage. Although BMT can cure X-SCID much of the time, current therapy is not 100-percent effective and has short-term and long-term toxicities.

Recent gene therapy trials have documented the efficacy of gene transfer in this disease, albeit with toxicity related to insertional mutagenesis. A new generation of self-inactivating (SIN) vectors has been developed which lack all enhancer/promoter elements of the LTR U3 region and are also devoid of all gamma retroviral coding regions. A SIN vector expressing the IL-2RG gene, pSRS11.EFS.IL2RG.pre* has been developed and has shown a reduction in mutagenic potential compared to LTR configuration in non-clinical studies. The current study is a phase I/II trial of somatic gene therapy for patients with SCIDX1. Inclusion criteria include patients in whom HLA-matched family donors are unavailable and for whom no readily available (defined as: within 6 weeks, with ability to transplant within 3 months) HLA identical (A,B,C,DR,DQ) related or unrelated donor is available or patients with an active, therapy-resistant infection or other medical conditions that significantly increase the risk of allogeneic transplant. Primary endpoints include immunological reconstitution defined as absolute CD3 cells of >300/µl and PHA stimulation index >50 at 6 months post infusion and the incidence of life-threatening adverse reactions related to the gene therapy procedure.

B. Written Reviews by RAC Members

Seven RAC members voted for in-depth review and public discussion of the protocol. Key issues included the serious questions that remain about the risks of gene transfer in patients with X-SCID using retroviral vectors, the need for further discussion of this novel vector (including the validity of the preclinical data), and concerns about the trial's inclusion criteria.

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

Noting that the preclinical animal data are not entirely satisfying, Dr. Fan suggested that, prior to initiating the proposed trial, the investigators should conduct a side-by-side comparison of the current vector with vectors of higher leukemogenic potential, for example, the SIN vector with the internal promoter and the original non-SIN vector used in previous trials. He asked the investigators whether they had considered approaches that could specifically eliminate the leukemias seen in previous trials, should they arise.

Dr. Federoff asked the investigators whether any other assays of mutagenic potential of the study product might predict human toxicity and whether any experiment would exclude the leukemic potential resulting from the forced expression of the IL2RG gene. He also asked whether the elongation factor-1 alpha (EF-1α) promoter might be too weak to support expression within transduced cells. Given the observation that two older participants in prior X-SCID trials failed to experience immunological reconstitution, he asked whether the inclusion criterion regarding age should be altered. He requested examples of the exclusion criterion "therapy-resistant infection."

Dr. Kodish requested that the investigators indicate the current survival chances for a patient who has had HSCT and who would be eligible for this trial and suggested that the RAC consider the relative risk-benefit ratio of gene transfer vs. HSCT in light of the risk of leukemogenesis. He asked for specification of who would make the decision that a potential research participant has no donor available and/or no ability to be transplanted within 3 months. Dr. Kodish asked the investigators to comment on the lack of a stopping rule for the appearance of AEs, especially leukemia. He also offered five suggested changes to the informed consent document.

Ad hoc reviewer Dr. Rosenberg asked the investigators to discuss the assays used to compare the levels of expression achieved with the EF-driven γc with that achieved with retroviral promoter sequences as well as the relationship between the transgene copy numbers achieved in the mouse studies and the goal for the human clinical trial. She asked whether secondary transplant studies had been performed or are planned using the EF-based vector and requested a discussion of analyses of clonal expansion conducted in the mouse experiments to assess reconstitution of immune function. Dr. Rosenberg asked whether tumors that developed in the control animals that were infused with cells containing the retroviral vectors were analyzed for the presence of common retroviral insertions. She queried how the target number of vector copies per cell in this proposed study compares with the copy numbers achieved in the two earlier trials conducted in France and England and whether there would be age guidelines for this trial based on data obtained from those two trials.

C. RAC Discussion

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

- Dr. Zaia asked how the investigators would implement the inclusion criteria. In particular, he requested that the inclusion criteria be completely transparent. He also asked how the investigators were planning to handle the ethical issue of inclusion of research participants who had failed therapy, because the individual could be more at risk by having to show a time-related event to participate in this trial.

- Dr. Cowan asked how the investigators would deal with those infections for which there are no treatments other than reconstituting T cells.

- Dr. Alland asked why gene transfer would be safer or faster compared with transplantation from a haploidentical mother in this infected group of patients who are not doing well.

- Dr. O'Reilly stated that haplotype disparate transplants can be done in the well or the sick without cytoreduction, and the result, at least in the early months of life, is equivalent to transplants using cytoreduction. Two issues remain to be tested—(1) the meaning of long-term reconstitution of B cells in the children who undergo gene transfer and (2) whether the transformational capacity of this vector is markedly reduced. Gene transfer advantages compared with transplantation could be significant when looking at the quality of life of these participant-children 5 or 10 years after dosing. If the reduction in transformation is as prodigious as postulated, then this gene transfer approach would be far superior to currently available treatments.

- Dr. Ertl noted that the investigators are assuming they will obtain the same results as in the French SCID trials except for a lower or nonexistent incidence of leukemia. However, it is equally

possible that there will be less B-cell and T-cell reconstitution and that some of the research participants will develop leukemia. Compared with currently available treatments, which are improving with early diagnosis, Dr. Ertl wondered whether this experiment should be imposed on an extremely vulnerable population—children.

- Dr. Federoff framed the discussion as follows: (1) This is still an experimental approach that constitutes gene *transfer* and not gene *therapy*, (2) the potential for this approach to have lower oncogenic transformative activity is a reasonable experimental protocol to undertake, (3) whether gene transfer could lead to a higher degree of B-cell reconstitution than has been the case in the absence of any type of chemotherapeutic application is unknown until an experimental protocol is undertaken, (4) this vulnerable population, for which other treatment options are available, should be carefully considered and measured with regard to inclusion and exclusion, and (5) evaluation of this protocol should be framed in terms of safety and not efficacy.

- Dr. Zaia suggested that the investigators flesh out the exclusion criteria to reassure the public that those who might benefit from a less risky treatment will be excluded from this trial so they can seek that less risky treatment.

- Dr. Kodish asked if there is an age below which this proposed approach would not be considered.

- Dr. Strome expressed his concern about the ethics of offering gene transfer to a population of children when, with current standard treatment, 60 percent will be relatively healthy (with treatment with IVIG) and 40 percent will likely have a chronic disease that may manifest itself 15 or 20 years in the future when possibly more effective treatment alternatives will be available.

- Both Dr. Rosenberg and Dr. Fan stated that, based on the *in vitro* data and the animal data, the likelihood that this vector has a lower potential for insertional activation is quite significant and warrants moving forward to a human trial.

- Dr. Cowan reiterated the dangers of exposing children to cytoreduction; children who receive high-dose chemotherapy risk sterility, nondevelopment of secondary teeth, and shorter stature. The attraction of this gene transfer approach is that cytoreduction is not necessary to achieve the same B-cell reconstitution results.

D. Investigator Response

1. Written Responses to RAC Reviews

Regarding available therapeutic approaches, the investigators reviewed the survival rates from the European registry and their interpretation that current data indicate that HCT from HLA-mismatched related donors (MMRDs) may not provide rapid and sufficient immune reconstitution in X-SCID infants with severe infections. Gene modification of autologous hematopoietic progenitor cells can be expected to provide a more rapid and robust immune reconstitution in these infants, thus improving survival. Data also indicate that, even for patients who do not have severe infections at the time of haploidentical HCT, significant complications and/or insufficient immune reconstitution are observed in a high proportion of patients, making haploidentical HCT a less than optimal therapeutic approach.

The lack of an appropriate donor for a potential participant—and therefore eligibility for this trial—will be decided by unanimous consensus of all site PIs and the overall study PIs. However, the investigators offered to add an external panel to the eligibility decision if the RAC believes that is necessary. In addition, the investigators plan to reevaluate eligibility criteria after the first five participants have been enrolled for a minimum of 3 years.

The investigators proposed that the protocol be stopped immediately and reviewed by the DSMB, the institutional review board, and the FDA if one of these two SAEs is observed: (1) any leukemia potentially related to provirus insertion or (2) death related to the experimental treatment.

The investigators proposed to maintain use of the term "gene therapy" because of the success of this experimental treatment to date—of the 20 patients with X-SCID treated by gene transfer in France and London, 18 are currently alive and showing good immune reconstitution. The protocol will be modified to note that 5 of those 18 children have experienced the serious side effect of leukemia related to the gene transfer.

Noting that two older research participants (15 and 20 years old) with X-SCID treated in London by gene transfer failed to attain immune reconstitution, the investigators nonetheless stated their belief that older age should not be an exclusion criterion for this trial. Reasons given included the limited experience with gene transfer in older children with X-SCID and that thymic aging *per se* does not preclude the ability to support thymopoiesis. It is possible—but not proven—that this therapy is more efficacious in younger individuals.

The investigators interpreted the available data as not supporting the hypothesis that γc is oncogenic, and one potential advantage of the proposed vector is that expression of γc is reduced compared with the vector used in previous clinical trials.

Regarding the strength of the EFS promoter, while lower levels of expression are detected compared to the LTR driven MFG vector, the level of transgene expression supported development of human T cells from patient derived CD34+ cells and reconstituted immunity in the mouse $\gamma c^{-/-}$ model.

The goal of the investigators is to achieve transduction efficiency of 30 percent to 40 percent; in previous human SCID studies, such efficiency results in the average copy number of 1 in peripheral T cells. Vector dosage in this trial should be similar to the dose in previous trials, since the investigators do not propose to change either the envelope protein or the culture conditions in the transduction protocol. Similarity of the vector dosage was an important consideration in favor of using a gamma retroviral SIN vector.

Preclinical studies included as part of the FDA filing were conducted to incorporate long-term observation and serial transplantation. In those studies, the investigators used the clinical vector proposed for this trial and saw no tumor formation associated with vector integration.

Although the use of suicide genes for safety may be attractive theoretically and was considered, the investigators decided against this approach because they wanted to replicate as much of the initial trial vector as possible. Theoretically, use of suicide genes such as thymidine kinase may cause an immune response to the vector. Four of the five (out of 20) initial research participants who developed T-cell leukemia in the previous trials are in remission and have maintained immunological function. It is possible that the use of suicide approaches might not eliminate the leukemia and might eliminate the transgenic cells to a degree that would eliminate the functional graft.

The investigators agreed to incorporate all of the suggested changes to the informed consent document.

2. Responses to RAC Discussion Questions

Regarding the inclusion criterion of having failed treatment, the investigators noted that the nature of the potential participant's infection is relevant. Some infections are rarely susceptible to treatment—for example, parainfluenza virus type 3 and adenoviral infections—so a time limit for inclusion in this trial would not be advisable for infants with SCID who have those infections. For potential participants with other infections in which the chances of cure or stabilization are much higher—for example, *Pneumocystis carinii* pneumonia or cytomegalovirus infection—it would be acceptable to stop treatment and wait for clinical conditions to improve before attempting experimental therapy. However, the personal judgments of all the physicians/PIs regarding inclusion should be paramount, as planned for this study, since no data strongly suggest that it is possible to define a time window by which one patient should be considered a treatment failure.

Potential participants who are well at the time of transplantation and do not have a matched sibling donor would not be immediately eligible for gene transfer. Those individuals should be given an opportunity to search for a matched unrelated donor, because the results of matched unrelated donor transplantation are now almost equivalent to the results achieved with matched sibling transplantation.

It has been estimated in the literature that approximately 50 percent to 60 percent of participants admitted into previous SCID trials had serious infections at the time of gene transfer.

The investigators stated that the inclusion criteria should be left somewhat vague because it is possible that drugs to treat the currently untreatable infections would become available and should be tested before a patient is considered eligible for gene transfer.

The investigators reiterated that any potential participant who has an HLA identical sibling will not be considered eligible for this gene transfer trial even if currently sick; this exclusion will be spelled out more clearly in the appropriate locations in the protocol.

The investigators offered to give serious consideration to the possibility that infants who are younger than 3 months who are well at the time of observation not be enrolled and eligible for gene transfer, because of the survival data presented by Dr. Buckley at this RAC meeting and because of similar data recently obtained by other groups.

The investigators agreed to use surrogate measurements for determining whether the graft is present; measuring whether the transgene is present provides some evidence that there may be some T-cell reconstitution. Another surrogate measure is that, always within 2 to 4 weeks of infusing the cells, NK cells appear transiently, which could provide a robust indication that the graft has been successful. A third surrogate measure is that, between 8 and 10 weeks after dosing, T cells are seen. Therefore, if none of these surrogate measures was seen by 12 weeks, that would be an indication for suggesting that the experiment was not successful and that the research participant should receive a haplodisparate transplantation.

E. Public Comment

No public comments were offered.

F. Synopsis of RAC Discussion and RAC Observations and Recommendations

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

<u>Preclinical Issues</u>

- If feasible, the investigators should develop an animal model that replicates insertional mutagenesis and use it to compare the leukemogenic potential of the SIN vector and the vector used in the clinical studies (MFG retroviral vector) that resulted in cases of insertional mutagenesis.

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

- HLA-identical donor transplantation remains the first-line treatment for X-SCID. Although haploidentical transplantation results in lower overall survival rates compared to HLA-identical transplantation, improved rates of survival are seen in haploidentical transplantations when they are done at an early age. As such, the inclusion/exclusion criteria should be modified as follows:
    - All individuals who have an available HLA-identical donor, even those with an active infection, should be excluded from enrollment.

  - Healthy infants with X-SCID who are younger than 3.5 months should be excluded because they should be treated with a haploidentical transplantation that offers proven efficacy at that age.

- Under the current exclusion criteria, potential participants who have "other conditions, which in the opinion of the PI or coinvestigators contra-indicate infusion of transduced cells" would not be eligible for this trial. These criteria should be refined to provide further guidance to the investigators in selecting participants and promoting uniformity.

- If there is no evidence of immune reconstitution and/or gene expression by 12 weeks after vector administration, a haploidentical transplantation should be offered. Plans should be developed to ensure that the haploidentical transplantation could be undertaken after the 12-week mark.

Ethical/Legal/Social Issues

The informed consent document should be revised as follows:

- The document should state that (1) the safety of the SIN vector has been established in preclinical models only, and (2) although the clinical efficacy of gene transfer for X-SCID has been seen in previous clinical trials, a different vector construct was used in those trials, and as such, there is no guarantee that a similar therapeutic effect will be achieved with the SIN vector.

- Due to this uncertainty about efficacy, the term "gene transfer" should be used instead of "gene therapy."

- The discussion of the alternative of haploidentical transplantation should be expanded to include specific information about the availability of haploidentical transplantation as well as data on survival and immune reconstitution in patients treated in the United States and Europe.

- The explanation of the risks of cancer due to insertional mutagenesis should be simplified.

Two of the RAC members had dissenting views. Dr. Ertl's dissent was based on safety concerns about the vector, specifically with respect to the risk of insertional mutagenesis. In her view, the preclinical studies did not result in sufficient data to justify proceeding to human studies and that studies in an *in vivo* model were needed to determine directly whether the SIN vector significantly reduced or eliminated the risk of insertional mutagenesis compared to the vectors used in the previous gene transfer trials, in which five children developed leukemia due to insertional mutagenesis. The RAC recommended that this be pursued but recognized that such a model may not be feasible and did not agree that the data developed to date were insufficient in assessing the SIN vector's potential to cause insertional mutagenesis.

Dr. Ertl also gave more weight to the uncertainties about the efficacy of the SIN vector given that patients may have a better chance with a haploidentical transplant. To help reduce this possibility, she suggested initially enrolling the first 2 or 3 subjects who meet the inclusion criteria, i.e. have an infection that is therapy-resistant but not enroll patients with a life threatening infection until the efficacy of the gene transfer is established. The assessment of the predicted clinical course of an infection in an individual patient is something that one may not be able to capture completely in inclusion/exclusion criteria and as currently envisioned the enrollment process would involve a clinical assessment of the patient.

Dr. Strome's concerns focused on whether the risks of gene transfer are outweighed by the potential benefits. He noted data presented at the meeting that indicate that SCID patients, including X-SCID patients, can achieve full immune reconstitution when haploidentical transplant is accompanied by preconditioning chemotherapy. However, such preconditioning is not without risks. The alternative, haploidentical transplant without conditioning leaves the majority of children with incomplete immune reconstitution, necessitating life-long use of immunoglobulin. Gene transfer could offer an alternative to preconditioning that might be safer and provide improved immune reconstitution if there was not the risk of leukemia from insertional mutagenesis by the vector. The ability of this new vector to offer improved

efficacy while reducing or eliminating the risk of this life threatening iatrogenic illness remains an open question that would be addressed by this trial. However, in Dr. Strome's assessment, risks of proceeding with this trial in a highly vulnerable population for which alternative therapies exist and informed consent is difficult is not outweighed by the benefits.

G. Committee Motion 5

Dr. Federoff summarized the comments and concerns of the RAC to be included in a letter to the investigators and the sponsor. It was moved that the RAC approve these summarized recommendations. The vote was 11 in favor, 2 opposed, 0 abstentions, and 2 recusals. Dr. Federoff stated that the concerns of Drs. Ertl and Strome would be included in the letter.

XII. Closing Remarks and Adjournment

Dr. Federoff thanked the RAC members and the OBA staff and adjourned the meeting at 12:50 p.m. on December 4, 2008.

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

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

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

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

Date: _____

_____
Howard J. Federoff, M.D., Ph.D.
Chair
Recombinant DNA Advisory Committee

Attachment I
Recombinant DNA Advisory Committee Roster

Chair

FEDEROFF, Howard J., M.D., Ph.D.
Executive President and Executive Dean
Georgetown University Medical Center
Building D, Room 120
4000 Reservoir Road, NW
Washington, DC 20007

Members

ALLAND, David, M.D.
Chief
Division of Infectious Disease
Professor of Medicine
New Jersey Medical School
University of Medicine and Dentistry of New Jersey
MSB A 920C
185 South Orange Avenue
Newark, NJ 07103

BARTLETT, Jeffrey S., Ph.D.
Principal Investigator
Center for Gene Therapy
The Research Institute
Nationwide Children's Hospital
Associate Professor of Pediatrics and of Molecular Virology, Immunology, and Medical Genetics
College of Medicine
The Ohio State University
700 Children's Drive, Room WA3016
Columbus, OH 43205-2696

BUCHMEIER, Michael J., Ph.D., M.S.
Professor
Departments of Molecular Biology and Biochemistry
Division of Infectious Disease
Department of Medicine
School of Medicine
University of California, Irvine
McGaugh Hall, Room 3205
Irvine, CA 92697-3900

ERTL, Hildegund C.J., M.D.
Director
Vaccine Center
The Wistar Institute
School of Medicine
University of Pennsylvania
3601 Spruce Street
Philadelphia, PA 19104

FAN, Hung Y., Ph.D.
Director
Cancer Research Institute
University of California, Irvine
Sprague Hall, Room 106
Mail Code 3905
Irvine, CA 92697

FLINT, Jane, Ph.D.
Professor
Department of Molecular Biology
Princeton University
Lewis Thomas Laboratory, Room 234
Princeton, NJ 08544

KAHN, Jeffrey P., Ph.D., M.P.H.
Maas Family Chair in Bioethics
Director
Center for Bioethics
University of Minnesota
Boynton Health Service Building, Room N504
410 Church Street, SE
Minneapolis, MN 55455-0346

KANABROCKI, Joseph A., Ph.D.
Assistant Dean for Biosafety
Associate Professor of Microbiology
Department of Microbiology
Biological Sciences Division
The University of Chicago
Cummings Life Science Center, Room 117
920 East 58th Street
Chicago, IL 60637

KIRCHHOFF, Louis V., M.D., M.P.H.
Professor
Departments of Internal Medicine (Infectious Diseases) and Epidemiology
Roy J. and Lucille A. Carver College of Medicine
University of Iowa
Bowen Science Building, Room 4-403
51 Newton Road
Iowa City, IA 52242

KODISH, Eric D., M.D.
F.J. O'Neill Professor and Chair
Department of Bioethics
The Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, OH 44195

ROIZMAN, Bernard, Sc.D.
Joseph Regenstein Distinguished Service Professor
Departments of Microbiology, and Molecular Genetics and Cell Biology
The University of Chicago
910 East 58th Street
Chicago, IL 60637

SHAH, Prediman K., M.D.
Director
Division of Cardiology
Atherosclerosis Research Center
Cedars-Sinai Medical Center
Suite 5531
8700 Beverly Boulevard
Los Angeles, CA 90048

SHAPIRO, Robyn S., J.D.
Professor and Director
Center for the Study of Bioethics
Medical College of Wisconsin
8701 Watertown Plank Road
Milwaukee, WI 53226-3548

SOMIA, Nikunj V., Ph.D.
Associate Professor
Department of Genetics, Cell Biology, and Development
Molecular Genetics Institute
University of Minnesota, Twin Cities
Jackson Hall, Room 6-160
321 Church Street, SE
Minneapolis, MN 55455

STROME, Scott E., M.D.
Professor and Chairman
Department of Otorhinolaryngology—Head and Neck Surgery
School of Medicine
University of Maryland
16 South Eutaw Street, Suite 500
Baltimore, MD 21201

WEI, Lee-Jen, Ph.D.
Professor
Department of Biostatistics
Harvard School of Public Health
Harvard University
677 Huntington Avenue
Boston, MA 02115

WILLIAMS, David A., M.D.
Chief
Division of Hematology/Oncology
Director of Translational Research
Children's Hospital Boston
Leland Fikes Professor of Pediatrics
Department of Pediatrics
Harvard Medical School
Karp Family Research Building, Room 07212.0
300 Longwood Avenue
Boston, MA 02115

YANKASKAS, James R., M.D., M.S.
Professor of Medicine
Division of Pulmonary and Critical Care Medicine
Department of Medicine
School of Medicine
The University of North Carolina at Chapel Hill
Thurston Bowles Building, Room 7011
Chapel Hill, NC 27599-7248

ZAIA, John A., M.D.
Professor and Chairman
Division of Virology
Beckman Research Institute
City of Hope
1500 East Duarte Road
Duarte, CA 91010-3000

Executive Secretary

CORRIGAN-CURAY, Jacqueline, M.D., J.D.
Executive Secretary
Recombinant DNA Advisory Committee
Medical Officer
Office of Biotechnology Activities
Office of Science Policy
Office of the Director
National Institutes of Health
U.S. Department of Health and Human Services
MSC 7985
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892-7985

OBA Director

PATTERSON, Amy P., M.D.
Director
Office of Biotechnology Activities
Director
Recombinant DNA Program
Recombinant DNA Advisory Committee
Office of Science Policy
Office of the Director
National Institutes of Health
U.S. Department of Health and Human Services
MSC 7985
6705 Rockledge Drive Suite 750
Bethesda, MD 20892-7985

Ad Hoc Reviewers and Speakers

BUCKLEY, Rebecca H., M.D.
James Buren Sidbury Professor of Pediatrics
Professor of Immunology
Departments of Pediatrics and Immunology
Duke University Medical Center
Jones Building, Room 363
Box 2898
Durham, NC 27710

COWAN, Morton J., M.D.
Professor of Pediatrics
Chief
Blood and Marrow Transplant Division
Children's Hospital
University of California, San Francisco
505 Parnassus Avenue
San Francisco, CA 94143-1278

O'REILLY, Richard, M.D.
Chairman
Department of Pediatrics
Memorial Sloan Kettering Cancer Center
1275 York Avenue, Box 139
New York, NY 10021

ROSENBERG, Naomi, Ph.D.
Professor
Department of Pathology
School of Medicine
Tufts University
Jaharis Building, Room 512
150 Harrison Avenue
Boston, MA 02111

Nonvoting Agency/Liaison Representatives

National Science Foundation
NSF Representative TBD

U.S. Department of Agriculture

JONES, Daniel D., Ph.D.
National Program Leader/Biotechnology
Cooperative State Research, Education, and Extension Service
U.S. Department of Agriculture
Waterfront Center, Room 3444
800 Ninth Street, SW
Washington, DC 20024

McCAMMON, Sally L., Ph.D.
Science Advisor
Biotechnology Regulatory Services
Animal and Plant Health Inspection Service
U.S. Department of Agriculture
4700 River Road, Unit 98
Riverdale, MD 20737

U.S. Department of Commerce

LEVIN, Barbara, Ph.D.
Project Leader
Biotechnology Division
National Institute of Standards and Technology
U.S. Department of Commerce
MSC 8311
100 Bureau Drive
Gaithersburg, MD 20899-8311

U.S. Department of Energy

DRELL, Daniel W., Ph.D.
Biologist
Life Sciences Division
Office of Biological and Environmental Research
U.S. Department of Energy
SC-72
19901 Germantown Road
Germantown, MD 20874-1290

U.S. Department of Health and Human Services

Office for Human Research Protections

BORROR, Kristina C., Ph.D.
Director
Division of Compliance Oversight
Office for Human Research Protections
U.S. Department of Health and Human Services
Tower Building, Suite 200
1101 Wootton Parkway
Rockville, MD 20852

Food and Drug Administration, Office of Cellular, Tissue, and Gene Therapies

TAKEFMAN, Daniel M., Ph.D.
Chief
Gene Therapy Branch
Division of Cellular and Gene Therapies
Office of Cellular, Tissue, and Gene Therapies
Center for Biologics Evaluation and Research
Food and Drug Administration
U.S. Department of Health and Human Services
HFM-720
1401 Rockville Pike
Rockville, MD 20852-1448

U.S. Environmental Protection Agency

FREDERICK, Robert, Ph.D.
Program Manager
Office of Research and Development
National Center for Environmental Assessment
U.S. Environmental Protection Agency
Mail Code 8623D
401 M Street, SW
Washington, DC 20460

MILEWSKI, Elizabeth, Ph.D.
Senior Biotechnologist
Office of Prevention, Pesticides, and Toxic Substances
U.S. Environmental Protection Agency
East Tower, Room 625
Mail Code 7201
401 M Street, SW
Washington, DC 20460

Liaison Representative

FAYL, Gilbert, Ph.D.
Secretary of External Affairs
European Academy of Sciences and Arts
Brussels, Belgium

Attachment II
Public Attendees

Luc Bereau, ActoGeniX NV
Rik Bleijs, National Institute of Public Health, The Netherlands
Decebal Bora, ActoGeniX NV
Fiona Cilli, ActoGeniX NV
Mary Ellen Conley, St. Jude Children's Research Hospital
Suk De Ravin, National Institute of Allergy and Infectious Diseases (NIAID)
Mark J. Federspiel, Mayo Clinic
Alexandra H. Filipovich, Cincinnati Children's Hospital Medical Center
Ying Huang, FDA, DHHS
Elizabeth Kang, NIAID, NIH
Donald B. Kohn, Children's Hospital Los Angeles
Derrick Lonz, National Institute of Public Health, The Netherlands
Harry L. Malech, NIAID, NIH
Barbara Matthews, ActoGeniX NV
Stacy McIntosh, Juvaris BioTherapeutics, Inc.
Thomas Monath, Juvaris BioTherapeutics, Inc.
Ray Myers, Mayo Clinic
Sung-Yun Pai, Children's Hospital Boston
Andrew Pekosz, Johns Hopkins University
Susan Radtke, Cincinnati Children's Hospital Medical Center
Donna R. Savage, Intelligent Fingers Writing & Editing
Jean Schoen, Eberlin Reporting Service
Mercedes Serabian, FDA, DHHS
Mona Siddiqui
Stephen T. Sonis, Brigham and Women's Hospital
Brian Sorrentino, St. Jude Children's Research Hospital
Lothar Steidler, ActoGeniX NV
John Warner, Juvaris BioTherapeutics, Inc.
Josiah Wedgwood, NIAID, NIH
Carolyn Wilson, FDA, DHHS

Attachment III
Abbreviations and Acronyms

ABL	animal biosafety level
ADA	adenosine deaminase
AE	adverse event
BL	biosafety level
BWG	Biosafety Working Group (a subcommittee of the RAC)
CD	Crohn's disease
CDC	Centers for Disease Control and Prevention, DHHS
CLDC	cationic liposome-noncoding plasmid DNA complex
DHHS	U.S. Department of Health and Human Services
DNA	deoxyribonucleic acid
DSMB	data and safety monitoring board
DUMC	Duke University Medical Center
E. coli	*Escherichia coli*
EF-1α	elongation factor-1 alpha
FDA	Food and Drug Administration, DHHS
GVHD	graft-versus-host disease
HA	hemagglutinin
HCC	hepatocellular carcinoma
HCT	hematopoietic cell transplantation
HCV	hepatitis virus type C
HEPA	high-efficiency particulate air
HLA	human leukocyte antigen
HPAI	highly pathogenic avian influenza
hTFF1	human trefoil factor 1
IFN	interferon
IFN-β	interferon-beta
IL-12	interleukin-12
IND	investigational new drug
ISATTAC	Intergovernmental Select Agents and Toxins Technical Advisory Committee
IV	intravenous
IVIG	intravenous immunoglobulin
L. lactis	*Lactococcus lactis*
MMRD	mismatched related donor
MTD	maximal tolerable dose
NIAID	National Institute of Allergy and Infectious Diseases, NIH
NIH	National Institutes of Health
NIH Guidelines	*NIH Guidelines for Research Involving Recombinant DNA Molecules*
NK	natural killer
OBA	Office of Biotechnology Activities, NIH
OD	Office of the Director, NIH
OM	oral mucositis
PAPR	positive air purifying respirator
PBMC	peripheral blood mononuclear cell
PI	principal investigator
PK	pharmacokinetic
RAC	Recombinant DNA Advisory Committee
RG	Risk Group
SAE	serious adverse event
SCID	severe combined immunodeficiency disease
SIN	self-inactivating
$TCID_{50}$	50 percent tissue culture infective dose

TPF	docetaxel plus cisplatin and fluorouracil
TREC	T-cell receptor excision circle
UCSF	University of California, San Francisco
USDA	U.S. Department of Agriculture
VSV	vesicular stomatitis virus
X-SCID	X-linked severe combined immunodeficiency disease