# RECOMBINANT DNA ADVISORY COMMITTEE (RAC)
# NATIONAL INSTITUTES OF HEALTH ( NIH)
# BETHESDA, MARYLAND
# June 18-19, 1998
# SUMMARY MINUTES

## I. Call to Order and Opening Remarks/Mickelson

Dr. Claudia A. Mickelson, Chair of the Recombinant DNA Advisory Committee (RAC), called the meeting to order at 9:00 a.m. on June 18, 1998. Notices of the meeting under the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* were published in the *Federal Register* on May 4, 1998 (63 FR 24712) and May 26, 1998 (63 FR 28514).

Dr. Mickelson noted that an action under the *NIH Guidelines* was promulgated in the *Federal Register* of May 11, 1998 (63 FR 26018); this action provides an optional electronic submission format for the registration of human gene transfer protocols with the Office of Recombinant DNA Activities (ORDA).

## II. Minutes of the March 10, 1998, Meeting
## Reviewers: Aguilar-Cordova, Mickelson

### Committee Motion 1

The RAC approved a motion made by Dr. Aguilar-Cordova and seconded by Dr. Louise Markert to accept the minutes of the March 10, 1998, RAC meeting (with the incorporation of minor editorial changes) by a vote of 8 in favor, 0 opposed, and no abstentions.

## III. Data Management
## Summary: Greenblatt (presented by Aguilar-Cordova)

To date, 244 human gene transfer protocols have been registered with ORDA including 30 gene marking protocols, 212 gene therapy protocols, and 2 non-therapeutic protocols. Therapeutic protocols include 23 for infectious diseases (all HIV-1), 33 for monogenic diseases, 147 for cancer, and 9 for other diseases/disorders (rheumatoid arthritis, coronary and peripheral artery disease, arterial restenosis, and cubital tunnel syndrome). Since the March 10, 1998, RAC meeting, the following nine protocols have been recommended for sole Food and Drug Administration (FDA) review: 9801-227, 9801-229, 9801-230, 9802-231, 9802-239, 9803-240, 9803-241, 9803-242, and 9804-243. The following protocols are to be reviewed at this meeting: 9802-232, 9802-235, 9802-236, 9802-237, 9802-238, 9804-244, and 9804-247. Fourteen amendments and four safety/adverse event reports were submitted to ORDA since the March 1998 RAC meeting.

### Committee Motion 2

The RAC approved a motion by Dr. Aguilar-Cordova and seconded by Dr. Macklin to accept the Data Management Report by a vote of 8 in favor, 0 opposed, and no abstentions.

## IV. Discussion on Gonadal Biodistribution of Gene Transfer Vectors/Mickelson

Dr. Mickelson provided an overview of the RAC's previous discussions on gonadal biodistribution of gene transfer vectors. At the December 15, 1997, RAC meeting, Drs. Steven Bauer and Anne Pilaro (FDA) reported the FDA's observation that multiple preclinical animal studies designed to assess vector biodistribution have demonstrated unexpected persistence of vector nucleic acid sequences in gonadal tissue. Presently, there is no information bearing upon the question of whether these sequences are intracellular or integrated. If intracellular, it is unknown whether these sequences are in gametes or somatic cells. Based on these limited data, the findings raise concern that administration of gene transfer vectors could lead to germ-line integration, a circumstance that would pose unknown risk to subjects participating in gene transfer clinical trials. Concurrently, the FDA indicated that sponsors are increasingly interested in gene therapy for less serious disease, earlier intervention before manifestations of disease, and gene transfer for augmentation or enhancement purposes. Under the limits of confidentiality, the FDA could not discuss further specifics of the observations.

In an effort to gain additional data related to these observations, the RAC recommended that a letter should be sent to all principal investigators of clinical gene transfer protocols and to all Institutional Biosafety Committees (IBCs) registered with ORDA (more than 400) requesting submission of all preclinical and clinical data related to this issue. ORDA received more than 80 responses to this request. Four responses indicated that vector sequences were detected in either the ovaries or testes in preclinical animal studies; however, the number of responses received was not representative of the number of clinical trials currently registered with ORDA.

The four responses indicating that vector sequences were detected in either ovaries or testes in preclinical animal studies are summarized as follows: (1) Peter T. Scardino, M.D., Baylor College of Medicine, Houston, Texas, stated that they published a paper documenting their preclinical data (Timme, T. L., et al., *Cancer Gene Therapy*, Volume 5, No. 1, 1998). Briefly, in murine experiments with adenoviral vectors expressing the Herpes Simplex Virus Thymidine Kinase (HSV-TK) gene, only 1 animal of 28 was found to have evidence of vector DNA present in testicular tissue by polymerase chain reaction (PCR) analysis. (2) Simon J. Hall, M.D., The Mount Sinai Medical Center, New York, New York, stated that in murine experiments, 1 out of 14 mice had vector sequences in testes after injection of an adenovirus expressing HSV-TK into the prostate. No vector DNA sequences were noted within sperm aspirated from the epididymis. (3) Jeffrey Holt, M.D., Vanderbilt University, Nashville, Tennessee, stated that after intraperitoneal and intraprostate injection of a retroviral vector in mice and rats, vector sequences were detected by PCR in ovaries and testes for up to four weeks. (4) Verma Fimbres, GenCell Division of Rhone-Poulenc Rorer, Inc., stated that they have studied the biodistribution of adenovirus-p53 sequences. After intratumoral administration in nude mice, a weak signal was detected in ovaries; after intratracheal administration in mice, the ovaries were positive at day 3 but negative at day 31; after intraperitoneal administration in cotton rats, they reported vector sequences in ovaries but not in testes.

Four responses indicated that no vector sequences were detected in human gonadal tissues in follow-up studies as follows: (1) Genetic Therapy, Inc. (Gaithersburg, Maryland), no vector sequences were detected in gonads in 45 samples from 45 patients treated with retroviral vectors. (2) Steven M Albelda, M.D., University of Pennsylvania, Philadelphia, Pennsylvania, no gonadal distribution was observed in four testicular samples analyzed from patients with mesothelioma treated with an adenovirus expressing HSV-TK in pleural space. (3) Chiron Corporation (Emeryville, California) reported no evidence of inadvertent germ-line transfer in samples of 118 patients infected with the human immunodeficiency virus (HIV) who received intramuscular injection of a retrovirus encoding the HIV *rev* gene. (4) Introgen Therapeutics, Inc. (Houston, Texas) reported no vector sequences were observed in the testes following administration of an adenovirus vector expressing the p53 tumor suppressor gene to three lung cancer

patients, and one patient with head and neck cancer. (In the latter patient, an initial positive finding in testes was subsequently found to be due to surface contamination of the samples during processing.)

During its March 10, 1998, meeting, the RAC recognized the need for improved detection methods and development of animal test systems to assess these observations further. At this meeting, the RAC recommended that a letter should be sent to theNIH Director advising that a Request for Applications should be issued for the development of vector-specific animal test systems that will provide qualitative and quantitative assessment of potential germ-line integration for specific classes of gene transfer vectors

Based on the complexity of the scientific questions, the RAC noted the need for a progressive approach to develop definitive biological information regarding this issue. Dr. Robertson Parkman, *ad hoc* expert (Children's Hospital of Los Angeles) suggested that a more appropriate method of addressing the issue of potential inadvertent germ-line integration would be to study the biology of germ-line integration in animals based on predefined criteria. Questions to be addressed should include: What is the frequency of integration? Are there gene delivery systems that are more likely to integrate than others? Do gonad and ovum barriers break down? Are specific routes of administration more likely to cause integration than others? What are the biological consequences of integration? Is there a correlation between integration and the type of disease/disorder?

Dr. Noguchi stated that, for protocols involving less serious disease, the "FDA has a problem addressing the issue; [the FDA] can only require emphasis on good informed consent." The RAC emphasized the importance of ensuring that Informed Consent documents include meaningful language regarding the implications of these findings that are as yet unknown. Dr. Parkman said that although it is reasonable to expect that the risk of germ-line integration is low for studies conducted to date, additional research is needed to assess the biology of germ-line integration. Dr. Noguchi agreed that research on the biology of germ-line integration would be extremely useful. Dr. Aguilar-Cordova agreed that such studies are important, but there is also a need to conduct toxicity studies separately. Dr. Mickelson suggested that the RAC should discuss the issue of animal models for biodistribution studies as a future agenda item.

Dr. Mickelson discussed potential changes to Appendix M, *Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Subjects (Points to Consider)* of the *NIH Guidelines*. The potential changes would provide guidance to the investigators regarding appropriate biodistribution studies for clinical protocols and issues that should be addressed in patient Informed Consent documents. Drs. Gordon, Ando, and Mickelson agreed to develop the proposed amendments for consideration at the September 1998 RAC meeting.

**V. Human Gene Transfer Protocol 9802-237 entitled: *Molecular Synovectomy by In Vivo Gene Transfer: A Phase I Trial***
**PI: Blake Roessler, University of Michigan**
**Reviewers: Ando, Lai, Lysaught**

**Protocol Summary**

Dr. Blake J. Roessler, University of Michigan Medical Center, Ann Arbor, Michigan, proposed conducting gene transfer experiments on eight patients (≥18 years of age) with rheumatoid arthritis (RA).pNGVL-TK is a plasmid expressing the herpes simplex virus thymidine kinase (HSV-TK) gene under the control of a modified cytomegalovirus (CMV) promoter/enhancer. This protocol is a Phase I dose-escalation study of intra-articular administration of pNGVL-TK plasmid DNA followed by systemic ganciclovir (GCV) for treatment of active rheumatoidsynovitis of the knees. This trial will study four doses ofpNGVL-TK plasmid DNA over a range of one and one-half logs (0.3 mg, 1.0 mg, 3.3 mg, 10.0 mg). A constant dose o

intravenous GCV (5 mg/kg twice daily for three days) will be used for each dose of pGNVL-TK plasmid DNA tested. The investigator proposes to study two patients at each dose of pNGVL-TK plasmid DNA. The three major goals of this Phase I trial are: (1) to establish that rheumatoid synoviocytes can be transfected *in vivo* using intra-articular administration of naked pNGVL-TK plasmid DNA, (2) to establish the safety of the plasmid-based TK/GCV intra-articular treatment, and (3) to identify biological effects specific to TK/GCV gene transfer.

**RAC Discussion**

The RAC recommended full public discussion of this protocol because it is the first proposed use of plasmid DNA in patients with chronic rheumatoid arthritis, a disease that is not life threatening and for which alternative therapies exist.

Drs. Ando, Lai, and Lysaught submitted prior written reviews to which the investigators responded in writing. In his written review, Dr. Ando raised several issues requiring further discussion: (1) vector biodistribution through systemic circulation, (2) exclusion of patients with anti-DNA antibodies, (3) inclusion of a discussion in the Informed Consent document about the risk-to-benefit ratios of alternative therapies, (4) transient and low-level gene expression, and (5) immunogenicity of viral TK.

Dr. Lai raised several issues in his written review: (1) The use of DNA/liposome complexes for preclinical studies and naked plasmid DNA in the clinical trial. (2) The low transduction efficiency of plasmid DNA, and whether the bystander effect will be significant enough to have a cytotoxic effect on synoviocytes? (3) the choice of intravenous GCV administration rather than intra-articular administration, and (4) the need to examine target cells for the presence of plasmid DNA.

Dr. Parkman was concerned that patients with prior HSV infection could develop an anti-TK immune response.

**RAC Recommendations/Comments**

Dr. Lysaught noted the well written Informed Consent document; this document could serve as a model fo other investigators to prepare their Informed Consent documents. She recommended a few specific changes including removal of the word "treatment," which is misleading for a Phase I safety study.

**VI. Human Gene Transfer Protocol 9802-232 entitled: *Gene Therapy for Myocardial Angiogenesis*.**
**PI: Jeffrey Isner, Tufts University (Douglas Losordo representing Isner)**
**Sponsor: N/A**
**Reviewers: Wolff, Rothenberg (presented by Wolff)**
***Ad hoc:* William Kraus, Duke University (presented by Wolff)**

**Protocol Summary**

Dr. Jeffrey M. Isner, St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, Massachusetts, proposed conducting gene transfer experiments on 30 patients (age≥21 years) with a history of angina pectoris. phVEGF165 is a plasmid expressing the cDNA of the human 165 amino acid residue isoform of vascular endothelial growth factor (VEGF) under the transcriptional control of a CMV promoter. Eligible subjects must have stable exertional angina and areas of viable, but underperfused myocardium, who are not optimal candidates for surgical or percutaneous revascularization. Clinical responses will be evaluated by serial studies performed before and after gene transfer, including dobutamine stress "SPECT"-sestamibi myocardial perfusion, contrast stress echocardiography, exercise

treadmill testing, and selective coronary arteriography. The protocol is a Phase I, single-site, dose-escalating, open-label study to determine the safety and bioactivity of directintramyocardial gene transfer of phVEGF165 in patients with symptomatic myocardial ischemia to reduce angina pectoris. The secondary objective is to determine the anatomic and physiologic extent of collateral artery development in patients receiving intramyocardial phVEGF165 gene transfer.

**RAC Discussion**

The RAC recommended full public discussion of this protocol because it is the first proposal involving direct DNA injection into the heart.

Ms. Rothenberg and Drs. Wolff and Kraus submitted prior written reviews to which the investigators responded in writing. Dr. Douglas W. Losordo, co-investigator, provided oral responses to additional questions during the meeting. Several issues were discussed at the meeting. The RAC noted that gene transfer with naked DNA in the heart is potentially less worrisome than gene transfer with viral vectors. The RAC expressed concern regarding the issue of risk versus benefit; it is uncertain whether the level of VEGF expression is sufficient to elicit a clinical response; there is some degree of risk associated with the surgical procedure. A question was asked about whether a control arm using an empty plasmid will be initiated. Dr. Losordo responded that such a control arm is not appropriate for the present protocol using surgical delivery of the plasmid DNA; it will be considered when the less invasive catheter-based delivery is developed.

**RAC Recommendations/Comments**

(1) The inclusion criteria should be modified; enrollment should be limited to subjects who have angina and objective evidence of myocardial ischemia despite "maximal medical therapy" because of the potential risk of morbidity related to the surgical procedure.

(2) The Informed Consent document should include a statement in the introduction about the importance of requesting an autopsy to assess the issue ofbiodistribution, and it should include a clear and understandable description of all surgical procedures.

(3) The Informed Consent document should clearly articulate the subjects responsibility for any costs associated with this study. An addendum should be added advising potential subjects that any treatment for short-term adverse effects related to participation in this study will be provided free of charge.

(4) The protocol should be amended to include follow-up studies to monitor for anti-VEGF antibodies.

**VII. Human Gene Transfer Protocol 9802-238 entitled:*Phase I/Phase II Study of the Effects of Ascending Doses of Adenovirus Mediated Human FGF-4 Gene Transfer in Patients with Stable Exertional Angina***
**PI: Joon Lee, University of Pittsburgh**
**Sponsor: Anthony Bourdakis, Berlex Laboratories, CA**
**Reviewers: Gordon (presented by Macklin), McIvor (presented by Macklin), Macklin**
***Ad hoc:* William Kraus, Duke University (presented by Macklin)**

**Protocol Summary**

Berlex Laboratories, Inc., Richmond, California, proposed to conduct amulticenter (up to 10 sites) gene transfer trial on a minimum of 48 and a maximum of 120 patients (30-75 years of age) with stable angina.

The study involves intra-arterial administration of Ad5FGF-4 to the heart via a standard coronary angiography catheter and/or a guiding catheter and subselective catheter. Ad5FGF-4 is an E1A and E1B-deleted human adenovirus serotype 5 with a hFGF-4 insert driven by a CMV promoter. The protocol is a Phase I/II, randomized, placebo-controlled, ascending-dose study in doses up to $10^{11}$ viral particles. Anti-ischemic effects will be evaluated by treadmill exercise test and by stress echocardiography at 4 and 12 weeks. Potential adverse effects due to FGF-4, the adenovirus vector, and the catheter will be evaluated. The objectives of the study are: (1) to evaluate safety and anti-ischemic effects of ascending doses ofadenovirus mediated hFGF-4 gene transfer in patients with stable exertional angina, and (2) to select the safe and effective dose(s) for a subsequent study.

**RAC Discussion**

The RAC recommended full public discussion of this protocol because it involves a new gene, human fibroblast growth factor-4 (hFGF-4), a new route of administration (via a catheter inserted into the coronary artery), and further discussion of the risk versus benefit considerations (less serious disease than previous cardiac trials).

Drs. Gordon, McIvor, Macklin, and Kraus provided prior written reviews, to which the sponsor responded in writing. At the meeting, Dr. Anthony Bourdakis (Berlex Laboratories, Inc.) and Dr. Robert L.Engler (University of California at San Diego, and a representative of Collateral Therapeutics, San Diego) provided oral responses during the RAC discussion.

Several issues were discussed by the RAC. One concern involved the potential for this adenovirus vector to induce an immune response. The RAC asked why the protocol excluded women with reproductive potential. The investigator responded that the exclusion is due to a concern regarding potential adverse effects of FGF-4 on the fetus. The RAC discussed the appropriateness of the placebo group in each dose cohort including nine active treatments vs. three placebo patients. The RAC reached no consensus on this issue.

**RAC Recommendations/Comments**

(1) The RAC suggested that additional preclinical studies should be conducted using preimmune animals to assess any potential inflammatory response, since most patients will have had prior adenovirus infections.

(2) Adenovirus antibody status is not included in the inclusion or exclusion criteria for this protocol, and should be assessed.

(3) The frequency of assessing serum FGF-4 levels should be increased to include daily monitoring between Day 1 and Day 7.

(4) The introductory paragraph of the Informed Consent document should be modified so that it clearly states that the protocol is a safety study with no therapeutic intent.

**VIII. Human Gene Transfer Protocol 9802-235 entitled:*A Dose Escalating Phase I Study of the Treatment of Malignant Glioma with G207, a Genetically Engineered HSV-1***
**PIs: James Markert, University of Alabama at Birmingham and MichaelMedlock, Georgetown University, D.C.**
**Sponsor: Sheryl Osborne, NeuroVir, Inc., Canada**

**Reviewers: Gordon (presented by Ando), Verma (presented by Ando), Juengst (presented by Ando)**
***Ad hoc:*** **Edward Wagner, University of California, Irvine (presented by Aguilar-Cordova)**

**Protocol Summary**

Dr. James Markert, University of Alabama at Birmingham, Birmingham, Alabama, and Dr. Michael Medlock, Georgetown University, Washington, D.C., proposed conducting gene transfer experiments on 24 patients (≥18 years of age) with malignant glioma. The vector, G207, was derived from the parental HSV-1(F) strain by deletions in both copies of the γ34.5 neurovirulence gene and a disabling insertion of the *E. coli LacZ* gene into the ICP6 region for use as an easily detectable marker, which allows for differentiation from HSV-1(F). The clinical strategy takes advantage of the virus' ability to infect and lyse cells. The first cohort will receive a single stereotactic injection of approximately 0.1 ml of G207 into a region of the tumor defined by magnetic resonance imaging (MRI). Additional cohorts will receive injections into multiple loci at doses ranging from $1 \times 10^6$ to $1 \times 10^9$ focus forming units. The primary purpose of the study is to obtain safety information in a small number of individuals (three patients per group), with successive groups receiving escalating doses of G207 after appropriate intervals for evaluation of safety. As a secondary objective, patients will be followed serially by MRI for potential clinical response to G207.

**RAC Discussion**

The RAC recommended full public discussion of this protocol because this study involves the first use of a replication competent HSV vector, a modified human pathogen, for human gene transfer research; concerns related to potential toxicity to normal brain cells; and concerns about a potential immune response to the foreign proteins, i.e., *ß-galactosidase* and viral TK.

Drs. Gordon, Verma, Juengst, and Wagner provided prior written reviews, to which the sponsor responded in writing. During the meeting, Ms. Osborne and Dr. Frank Tufaro (NeuroVir, Inc.) and Dr. James Markert (University of Alabama at Birmingham) provided oral responses during the RAC public discussion.

Specific issues discussed by the RAC included the biological basis of selective tumor cell lysis caused by injection of G207. The G207 shows greatly enhanced replication in dividing cells compared with resting or non-dividing cell lines. The sponsor explained that the specificity for brain tumor cells was mainly due to deletion of both copies of the γ34.5 neurovirulence gene. The mechanism of action of the gamma 34.5 neurovirulence genes is not well understood. A disabling insertion of the *E. coli LacZ* gene into the ICP6 (viral ribonucleotide reductase) region provides an easily detectable marker, which allows for differentiation from the parental laboratory strain, HSV-1(F). Safety studies in the Aotus monkey demonstrated no toxicity. The precise mechanism for tumor cell specificity is not completely understood.

Other issues discussed included the potential for an inflammatory response to G207 when injected into the closed space of the brain, the immune status of the patients to HSV, the potential for virus reactivation, and the potential antigenicity of vector expression of the foreign bacterial *LacZ* gene. The RAC applauded the inclusion in the Informed Consent document of obtaining a Durable Power of Attorney in the event that a patient's decision-making ability is impaired following participation in the study. The sponsor and investigators responded to all of the questions raised by the RAC.

**RAC Discussion/Comments**

Based on the discussions, the RAC was satisfied with the responses provided by the investigators and sponsor; therefore, there were no specific recommendations.

**IX. Germ-line Gene Therapy**

Dr. Louise Markert noted the recent conference held at the University of California Los Angeles (UCLA) on March 20, 1998, on the subject of germ-line gene therapy. She raised the issue of whether the *NIH Guidelines* should be amended so that the RAC could begin to entertain the issue of germ-line gene transfer. Currently, the *NIH Guidelines* state: "RAC will not at present entertain proposals for germ-line alterations but will consider proposals involving somatic cell gene transfer. The purpose of somatic cellgene therapy is to treat an individual patient, e.g., by inserting a properly functioning gene into the subject's somatic cells. Germ-line alteration involves a specific attempt to introduce genetic changes into the germ (reproductive) cells of an individual, with the aim of changing the set of genes passed on to the individual's offspring."

Dr. Parkman stated that the RAC could initiate a process by which *ad hoc* experts are invited to "educate" both the committee and the public on the scientific, safety, and ethical implications of germ-line research. However, he cautioned against revising the *NIH Guidelines* regarding this issue. For the public record, Dr. French Anderson (University of Southern California, Los Angeles) stated that the RAC should not change the wording of the *NIH Guidelines* nor initiate the discussion of entertaining germ-line gene transfer proposals. Public discussion of this issue could be misinterpreted as an endorsement to proceed with such trials. Dr. Lysaught commented that the RAC should not give the appearance of being proactive regarding its "entertainment" of germ-line gene transfer protocols. Dr. Noguchi stated that the FDA welcomes public discussion of the issue before such protocols are submitted, noting that "we cannot ban anything." He encouraged the RAC to establish an appropriate mechanism to conduct public discussion of the issues without the appearance of endorsement. Dr. Aguilar-Cordova stated that the RAC is the appropriate forum to discuss the implications of germ-line gene transfer research.

The RAC endorsed Dr. Parkman's proposal to invite expert speakers as part of an ongoing education process and in accordance with its mandate to ensure public awareness of the scientific, safety, and ethics issues related to germ-line gene transfer. However, the RAC agreed that ***such discussions should not be viewed as an endorsement of germ-line gene transfer*** and that the intent of this process should be clearly articulated to the public, perhaps as a statement published in the *Federal Register*.

**X. Human Gene Transfer Protocol 9804-244 entitled: *A Phase I Study Using Direct Combination DNA Injections for the Immunotherapy of Metastatic Melanoma*.**
**PI: Patrick Walsh, University of Colorado**
**Reviewers: Louise Markert, Macklin**
***Ad hoc:*** **Robertson Parkman, Children's Hospital of Los Angeles**

**Protocol Summary**

Dr. Patrick Walsh, University of Colorado Health Sciences Center, Denver, Colorado, proposed conducting gene transfer experiments on 18 patients (≥18 years of age) with metastatic melanoma. The therapeutic DNA/liposome formulation, C192, contains equal weights of the purified pMB287 plasmid expressing the human Interleukin-2 (IL-2) cDNA and pMB288 plasmid expressing the superantigen staphylococcus enterotoxin B (SEB). Both of the gene inserts are expressed under the control of a CMV promoter. This protocol is a Phase I study to evaluate the safety of C192 in subjects with metastatic melanoma. Three subjects will receive one of six escalating doses (10, 100, 250, 500, 1,000, and 2,000

µg) of C192. Subjects will receive direct injection of the plasmid DNA coding for hIL-2 and SEB into cutaneous melanoma metastasis. Subjects will also be monitored for any potential clinical effect at the site of injection and local or distant mestastases.

**RAC Discussion**

The RAC recommended full public discussion of this protocol because this study represents the first use of the gene encoding the superantigen SEB in a clinical trial.

Drs. Louise Markert, Macklin, and Parkman provided written reviews to which the investigator responded in writing. At the meeting, Dr. Walsh provided oral responses during the RAC discussions. The RAC noted that the protocol was well written, and that the investigator satisfactorily addressed the majority of questions raised during the prior written review.

Dr. Parkman recommended that cytotoxic T lymphocyte (CTL) assays should be conducted to assess the immune response of T cell precursors. The investigator presented preclinical data demonstrating the lack of CTL response. However, Dr. Parkman noted that the preclinical studies were conducted using a combination of granulocyte-macrophage colony stimulating factor (GM-CSF) and SEB rather than the proposed combination of IL-2 and SEB.

The issue of local immunotherapy on distant metastases was discussed. The RAC suggested that enrollment of patients with at least two cutaneous lesions might allow assessment of the effects of vaccination on distant metastases. The investigator responded that the primary objective of this Phase I study is to assess safety with the additional endpoint of CTL assays to assess immune response; inclusion of patients with distant metastases will be considered in Phase II studies.

**RAC Recommendations/Comments**

(1) The RAC recommended that the Informed Consent document should be modified for the purpose of clarifying: (a) the use of autologous tumor cell lines, and (b) the patient financial responsibility for any costs associated with treatment of potential adverse events. The investigator agreed to clarify these issues in the Informed Consent document.

(2) The RAC recommended that the protocol should be amended to include evaluation of subjects' circulating T cell repertoire.

**XI. Compensation for Injured Research Subjects**

In response to the RAC's earlier discussion on the issue of compensation for costs arising from research-related injuries, Dr. Melody Lin (Office for Protection from Research Risks (OPRR)) distributed an article on this subject published in the *Journal of American Medical Association* on June 17, 1998 (Vol. 279, No. 23, page 1854). Dr. Parkman stated that the RAC discussed this issue previously. At that time, the RAC submitted a position paper to former NIH Director, Dr. Bernadine Healy, recommending the indemnification of subjects injured in the course of gene therapy research.

**XII. Human Gene Transfer Protocol 9802-236 entitled: *A Phase I Study of the Intraprostatic Injections of CN706, a Prostate-Specific Antigen Gene-Regulated Cytolytic Adenovirus in Patients with Locally Recurrent Cancer Following Definitive Radiotherapy*.**
**PI: Jonathan Simons, Johns Hopkins University**
**Sponsor: Dan Henderson, Calydon**

**Reviewers: Ando, Aguilar-Cordova, Juengst (presented by Ando)**

**Protocol Summary**

Dr. Jonathan W. Simons, Johns Hopkins University School of Medicine, Baltimore, Maryland, proposed conducting gene transfer experiments on up to 30 patients (≥18 years of age) with recurrent or persistent carcinoma of the prostate. CN706 is an attenuated, replication-competent adenovirus that has been genetically modified by inserting the 2.2 kb fragment containing the promoter and enhancer elements of the cloned prostate specific antigen (PSA) gene to a region upstream of the E1A gene of the virus. The gene-modified adenovirus replicates preferentially in human PSA-producing prostate cells.

Preclinical studies of CN706 demonstrate the generation of an oncolytic infection in PSA-producing cells and xenograft tumors. Five cohorts of three subjects will receive two courses (Days 1 and 4) of CN706 at one of five dose levels. The total dose, in viral particles, will depend upon volumetric assessment of the prostate. Doses will range from $1 \times 10^{10}$ to $1 \times 10^{12}$ particles per 3-5 cc of prostate volume. Subjects will receive up to 10 injections of CN706 using a transperineal approach. The primary objective of this study is to determine the maximum tolerated dose (MTD) of CN706 when administered by local injection into the prostate. Secondary objectives include evaluation of antitumor activity, time to disease progression, systemic bioavailability and distribution, and monitoring of the immune response.

**RAC Discussion**

The RAC recommended full public discussion of this protocol based on the following: (1) this protocol represents the first use of a replication-competent adenovirus, (2) the protocol involves the use of a prostate-specific promoter to target gene expression, and (3) the vector will be administered to a site anatomically close to germ cells.

Drs. Ando and Juengst provided prior written reviews, to which the investigator responded in writing. At the meeting, Drs. Simons and DeWeese provided oral responses to RAC questions. The RAC noted that the investigators responded satisfactorily to all of the RAC's questions contained in the written reviews.

The RAC discussed the observed dose-response curve resulting from the balance of virus-induced cell lysis and elimination of infected cells mediated by CTL responses. The RAC discussed whether this balance could be affected by adenovirus preimmunization. The RAC inquired about the replication specificity of CN706, noting that at high doses CN706 induces widespread pathology in Copenhagen rats. The RAC discussed the issue of whether a therapeutic window exists that will produce a favorable therapeutic index in the prostate. The investigator presented additional data demonstrating that the specificity of CN706 oncolytic activity is based on the vector design and anatomic delivery to the prostate.

The RAC discussed the potential for CN706 biodistribution to gonadal cells, noting the cotton rat and Copenhagen rat biodistribution studies.

**RAC Recommendations/Comments**

The RAC recommended that the Informed Consent document should be modified to: (1) include information explaining the importance of conducting an autopsy in the event of death. This notification that an autopsy will be requested should include a clear explanation regarding the need to obtain gonadal tissue for assessment of virus DNA integration into germ cells; (2) request permission to archive gonadal tissue as part of the surgical management of disease. Archived tissue will be valuable for assessing potential viral DNA integration into gonadal cells. Although the present technology is not yet fully

developed to assess whether integration occurs in germ cells or adventitious cells of sperm samples, it is anticipated that such assays will be available in the near future; (3) clarify the issue of compensation for subjects who could potentially be injured as a result of their participation in the study and any financial responsibility for medical costs.

**XIII. Functions of the RAC**

At the conclusion of the discussion of Protocol 9802-237 on the first day of the meeting, the RAC stated its intent to send a letter to PIs,IRBs, IBCs, OPRR, and the FDA following RAC discussion of a protocol. The letters will inform relevant parties of the RAC discussion, including remaining issues that should be addressed and areas of concern, and highlight positive aspects of the study design. The RAC noted that such letters will be useful to the IBCs' consideration of future gene transfer clinical trials and will assist theIRBs during annual review of the study. A motion adopting this policy was made by Dr. Ando and seconded by Dr. Gordon during the first day's discussion. The motion passed by a vote of 6 in favor, 1 opposed, and 1 abstention.

On the second day of the meeting, the RAC discussed future functions of the committee. MsKnorr provided background on previous discussions on this issue. During the March 1998 RAC meeting, Dr. Lana Skirboll (NIH Associate Director for Science Policy) recommended that the RAC begin development of a vision statement that would articulate its roles and responsibilities in response to the recently implemented changes regarding NIH approval of human gene transfer protocols. Once developed, this statement could be published in the *Federal Register*.

Members expressed varying viewpoints regarding future RAC functions. Suggestions included: (1) conducting pre-meeting reviews of protocols with reports to the full RAC, so that principal investigators and sponsors would not have to attend RAC meetings; (2) clarifying the criteria used to decide which protocols will be reviewed at regularly scheduled public meetings; (3) increasing emphasis on high-profile issues, such as germ-line and *in-utero* research, without reviewing individual protocols; (4) establishing standards for Phase I and Phase II clinical trials, including issues related to study design; (5) discussing the use of control arms; and (6) retaining the current format and continuing to review individual protocols.

Dr. Mickelson said that RAC review of the individual protocols was useful, both for the identification of specific research design issues and for public awareness that will ensure continued progress in the field. She noted that issues relating to Informed Consent documents were the most difficult to identify without protocol review. One problem, however, is that only those protocols undergoing full review have the benefit of Informed Consent document review. She suggested that the RAC explore mechanisms by which all Informed Consent documents are scrutinized to optimize patient understanding of all aspects of the research process and procedures.

Dr. Noguchi said that the public benefits significantly from RAC discussion, and that very few sponsors view this process as a waste of time. He said several issues were worth discussion by the full RAC, and he suggested that some issues are more worthy than others, e.g., safety concerns and partial correction issues surrounding *in utero* research and germ-line research. Dr. Aguilar-Cordova said the RAC was an education and discussion body, and that members should review the RAC statement of purpose to resolve questions about the functions of the RAC.

Issues raised in this discussion will be considered by the RAC in drafting a vision statement.

**XIV. Human Gene Transfer Protocol 9804-247 entitled:*A Phase I Safety and Dose Escalation Trial of Autologous Transfected Human Fibroblasts Producing Human Factor VIII in Patients with***

***Severe Hemophilia A***.
**PI: David Roth, Harvard Medical School**
**Sponsor: Kurt Gunter, Transkaryotic Therapies, Inc., MA**
**Reviewers: Verma (presented by Mickelson), Mickelson**
***Ad hocs:*** **Robertson Parkman, Children's Hospital of Los Angeles and Haig Kazazian, University of Pennsylvania (presented by Mickelson)**

**Protocol Summary**

Dr. David R. Roth, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, Massachusetts, proposed conducting gene transfer experiments on nine subjects (≥13 years of age) with severe hemophilia A. A plasmid expressing human factor VIII (hFVIII) is used to transfect autologousfibroblasts. The cloned DNA encodes a hFVIII gene in which the B domain has been deleted (BDD hFVIII). The modified hFVIII gene has been cloned into a pBR322-based plasmid.

The plasmid also contains sequences designed to maximize the expression of BDD hFVIII in human fibroblasts, as well as a selectable *neo*$^R$ gene. Dermal fibroblasts will be isolated by biopsy and expanded in culture. Expanded fibroblasts will be transfected by electroporation with the plasmid encoding hFVIII, and implanted via laparoscopy. Three subjects will be entered into each cohort; each cohort represents escalating doses between 1 x $10^8$ and 4 x $10^8$ fibroblasts. The objective of this study is to investigate the safety of non-virally transfected autologous human fibroblasts producing hFVIII when implanted within the peritoneum of hemophilia A patients.

**RAC Discussion**

The RAC recommended full public discussion of this protocol because it represents a new disease, new gene (BDD hFVIII), and new delivery method (transfected fibroblasts into the omentum).

Drs. Verma, Parkman, Mickelson, and Kazazian provided prior written reviews, to which the sponsor responded in writing. At the meeting, Dr. Roth (Beth Israel) and Drs. Selden andTreco (Transkaryotic Therapies, Inc., Cambridge, Massachusetts) provided oral responses to RAC questions. The sponsor and the investigators satisfactorily responded to RAC questions in the public session. The sponsor previously requested a closed session to discuss proprietary information in case the RAC asked questions that required discussion of proprietary issues.

Dr. Anderson objected to holding a closed session and reminded the RAC and the study sponsor that one of the committee's primary purposes is public accountability. He said that holding any discussion closed to the public would be contrary to the purposes and tradition of the RAC. Dr. Parkman said he had one question that was based on proprietary information submitted by the sponsor. The sponsor, after a brief private discussion with Dr. Parkman, agreed to respond publicly to his question. As a result, the RAC conducted the entire discussion of this protocol in public. Speaking as an industry representative, Mr. Steven Kradjian (Vical, San Diego) applauded the sponsor's willingness to maintain the public discussion, emphasizing the importance of ensuring public confidence.

Specific issues discussed by the RAC included the biology of fibroblasts transduced with hFVIII. The RAC asked if the transduced cells would produce and process the hFVIII protein differently from the natural protein and the possibility of mediating CTL and antibody responses. The RAC discussed the use of appropriate preclinical animal models. The investigators stated that they are beginning to develop a canine model for Hemophilia A-factor VIII, which is a more appropriate model than the factor VIII gene

knock-out murine model.

The RAC asked whether genotype analysis of patients would be valuable for the study. The investigators responded that such genotyping has limited value for this clinical study. The Informed Consent document has been amended to include discussion of the surgical removal of transplanted fibroblasts, if necessary. The RAC noted the relatively high monetary compensation for participation in the trial. Dr. Macklin noted that the Informed Consent document is clear, lucid, complete, and is written in a language understandable by the patients.

**RAC Recommendations/Comments**

The RAC recommended that the protocol be amended to include a stopping rule such that the trial will be terminated if two or more subjects develop either a CTL or antibody response to hFVIII.

**XV. Future Meeting Dates**

The next RAC meeting will be September 24-25, 1998, at NIH, Building 31C, Conference Room 10, Bethesda, Maryland. The next NIH Gene Therapy Policy Conference (GTPC) will be on the topic of *in utero* gene therapy, and has been rescheduled for December 10, 1998, in Bethesda, Maryland. Previously, the date for this GTPC was September 24, 1998. The December GTPC will be followed by the RAC meeting on December 11, 1998, at NIH Building 31C, Conference Room 10, Bethesda, Maryland.

**XVI. Adjournment**

Dr. Mickelson adjourned the meeting at 3:15 p.m. on June 19, 1998.

**Note:** This summary is based on notes obtained from ORDA staff. More detailed information about the RAC meeting will be available in the minutes of this meeting; however, the approved June 18-19, 1998, RAC minutes will not be available until after the September 25, 1998, RAC meeting. **Actions approved by the RAC are considered *recommendations* to the NIH Director; therefore, actions are not considered final unless approved by the NIH Director.**

The ORDA Web Site is: http://www4.od.nih.gov/oba/

The FDA Web Site for the *Guidance for Industry, Guidance for Human Somatic Cell Therapy and Gene Therapy* is: www.fda.gov/cber/guidelines.htm

July 6, 1998