DEPARTMENT OF HEALTH & HUMAN SERVICES

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May 7, 2001

Neal Nathanson, M.D.
Vice Provost for Research
215 College Hall
University of Pennsylvania
Philadelphia, PA 19104-6381

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1025

Research Project: "Recombinant Adenovirus Gene Transfer in Adults with Partial Ornithine Transcarbamylase Deficiency"
Principal Investigator: Steven Raper, M.D.
U. Penn. Study Number: 0366

Research Project: "Treatment of Advanced CNS Malignancy with Recombinant Adenovirus H5.010RSVTK: Phase I Trial"
Principal Investigator: Jane B. Alavi, MD
U. Penn. Study Number: 03702

Research Project: "Phase I Trial of AdRSVtk Virus with Ganciclovir in Patients with Unresectable Malignant Mesothelioma"
Principal Investigator: Daniel Sterman, MD
U. Penn. Study Number: 3587

Research Project: "Phase I clinical Trial Utiliting Gene Therapy for Limb Girdle Muscular Dystrophy..."
Principal Investigator: Hansell Stedman, MD
U. Penn. Study Number: 2664

Research Project: "Treatment of Recurrent or Progressive Malignant Glioma with a Recombinant Adenovirus Expressing Human Interferon Beta"
Principal Investigator: Stephen Eck, MD
U. Penn. Study Number: 1681

Research Project: Gene Therapy of CF Lung Disease using a Third Generation Adenovirus: A Phase I Trial
Principal Investigator: Ronald Rubinstein, MD
U. Penn. Study Number: 1821

Dear Dr. Nathanson:

The Office for Human Research Protections (OHRP), formerly the Office for Protection From Research Risks (OPRR), has reviewed your report of March 10, 2000, regarding the above referenced research conducted at University of Pennsylvania (U. Penn.). We apologize for the delay in responding to your report.

Based upon its review, OHRP makes the following determinations.

A. Finding Regarding Research Project: "Recombinant Adenovirus Gene Transfer in Adults with Partial Ornithine Transcarbamylase Deficiency"

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(4)(iii) require that the Institutional Review Board (IRB) review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. OHRP finds that for the protocol "Recombinant Adenovirus Gene Transfer in Adults with Partial Ornithine Transcarbamylase Deficiency" (OTCD) the following protocol changes were implemented without IRB approval:

(a) Failure to promptly report Grade III toxicities to the IRB and FDA and receive FDA and IRB approval before proceeding to cohort five after Grade III toxicities occurred, as required by the IRB approved protocol.

(b) Failure to modify the protocol and get IRB approval to reflect new risk factor exclusion criteria.

Corrective Action: OHRP acknowledges U. Penn.'s statement that planned education and training of Institute for Human Gene Therapy (IGHT) research personnel should greatly reduce the likelihood of such occurrences in the future. OHRP also notes U. Penn.'s plans to develop standard operating procedures to ensure that regulatory and protocol reporting requirements are strictly observed, and to give IRB members and staff regular training in procedures for reviewing and responding to reports of serious adverse events, with an emphasis on the requirement for review by the convened IRB. OHRP finds that these corrective actions adequately address this finding and are appropriate under the U. Penn. Multiple Project Assurance.

B. Additional Concerns and Questions Regarding the OTCD Study

(2) OHRP is concerned that when reviewing protocol applications, the IRB often appeared to lack sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. For example, OHRP notes the following:

(a) A revised protocol submitted for continuing review on August 11, 1997 changed the inclusion criteria in the OTCD study from <50 micromolar plasma ammonia to <70 micromolar. Although this modification was in the revised protocol that was approved by the IRB, it was not in the summary of changes to the protocol. Although U. Penn. stated to FDA that "the investigators did not believe that the change for 50 to 70 represented a material difference" other minor changes in the protocol were listed in the summary (such as reformatting and changing a statement from "to confirm transduction" to "determine if there has been transduction").

(b) A packet of materials distributed to prospective subjects and their families for the OTCD study was not reviewed and approved by the IRB.

Please respond.

(3) OHRP is concerned that the meaning of the inclusion/exclusion criterion regarding ammonia levels was unclear. The FDA felt that one subject did not meet the criterion since his plasma ammonia levels were 91- 114 micromolar during the hospitalization period before the study drug was administered. The protocol stated that the levels must be below 70 "prior to infusion of the study drug." U. Penn. contends that the "protocol did not require that a particular amount of ammonia level exist immediately before infusion." One subject's ammonia levels had been measured at 45 micromolar three months prior to infusion. Version 1.0 of the protocol and the revised grant application submitted to FDA in March of 1998 stated that "plasma ammonium levels must be <50 micromolar **at the time of the study**." (Emphasis added.) Please respond.

(4) OHRP is concerned that the informed consent documents reviewed and approved by the IRB for the OTCD study may have failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(1):

(i) An explanation of the purposes of the research. The informed consent document stated that "[t]he gene therapy process involves the following steps: ....(3) the virus carries the OTC gene into your liver cells. (4) in your liver cells the OTC gene produces the OTC enzyme that is missing in OTC deficiency." Other gene therapy informed consent documents proposed by

this investigator had similar language. This appears to imply that the investigators knew what would happen in this trial. Also, the informed consent documents refer to it as "therapy" when there is no knowledge that this Phase I trial would be therapeutic.

(ii) A complete description of the procedures to be followed, and identification of any procedures which are experimental.

– The description of the angiography for the delivery of gene therapy and radiation exposure from the angiography were not clearly described in informed consent documents approved by the IRB after 1997.

– An ECG is listed in version 4.0 of the protocol, but is not mentioned in the informed consent document.

– A November 6, 1996 request to amend the protocol included an additional blood draw to develop a patient cell line to do a CTL response. The January 1999 grant application "Gene Therapy for Inborn Errors of Urea Synthesis" included this blood draw and cell line development, but it was not in the informed consent document.

(b) Section 46.116(a)(2): A description of the reasonably foreseeable risks and discomforts to the subject.

– There are inconsistencies between the study consent form and the liver biopsy consent form. The study informed consent document stated "[t]here is also a very small risk (1 in 10,000) of serious unpredicted complications which can include death." However, the liver biopsy informed consent document stated "...there have been reports of serious, unpredicted complications that include death (1/5000)."

– The informed consent document stated "by giving the virus directly into the right side of the liver, we hope to obtain the maximal effect of the gene in the liver and to keep to a minimum any exposure of left-sided liver cells and non-liver cells to the virus." There was no evidence from animal studies that this would be the case. The revised grant application submitted to FDA in March of 1998 stated that biopsies of baboons transduced with the second generation vector via the hepatic artery showed liver toxicity in the targeted and nontargeted lobes of the liver.

Please respond.

(5) U. Penn. stated "As OTCD consent forms were updated from time to time, with IRB approval, to reflect modifications in the study procedures, patients who had already executed valid consent forms but had not yet completed all of the study procedures often were asked to sign the updated forms as well." The word "often" implies that sometimes subjects were not given updated informed consent documents to read and sign. Please clarify.

(6) In response to FDA's observations regarding the OTCD study, U. Penn. stated that "[a]lthough IHGT fully and properly performed its monitoring obligations in these respects, it has not implemented a formal mechanism for independently monitoring compliance with the numerous administrative requirements applicable to the OTCD study. IHGT believes that establishing such a system would address most of the issues raised [by FDA regarding lack of SOPs and monitoring]..." Has U. Penn. instituted such a system? Please provide OHRP with a summary of this system, if it exists or is being planned.

(7) HHS regulations at 45 CFR 46.116 state that no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject. An article that appeared October 25, 1996 in the Philadelphia Inquirer noted that Drs. Wilson and Batshaw attended the national meeting of the National Urea Cycle Foundation, in which they described their study and asked for volunteers. The article stated that they drew blood at that meeting "to identify carriers and possible test subjects." It is not clear if informed consent was obtained as there are no informed consent documents for simple blood draws (the screening informed consent document was much more extensive.) Please clarify. In your response, please include (i) a copy of the IRB-approved informed consent document for this screening for prospective subjects; and (ii) clarification as to whether the IRB approved this subject recruitment procedure.

C. Findings Regarding U. Penn.'s System for Protecting Human Subjects

(8) HHS regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures to specific research categories published in the Federal Register at 63 FR 60364. OHRP finds that use of expedited review by the IRB has not been restricted to these categories. In specific, OHRP finds that the IRB inappropriately used expedited procedures for conducting continuing review prior to at least 1997. OHRP recommends that documentation for initial and continuing reviews that are conducted utilizing expedited review procedures include citation of the specific permissible categories (see 63 FR 60364) justifying the expedited review.

(9) HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings be in sufficient detail to show actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues

and their resolution. OHRP finds that prior to 1998 IRB minutes often failed to meet these requirements. Furthermore, OHRP notes that IRB actions were not documented separately for each individual protocol.

(10) HHS regulations at 45 CFR 46.110(b) requires that expedited review be carried out by the IRB chair or by one or more experienced reviewers designated by the chairperson from among members of the IRB. OHRP finds that expedited review was sometimes carried out by an IRB staff member, not a member of the IRB.

(11) OHRP finds that IRB members were not advised of expedited approvals of minor changes in research protocols as required by HHS regulations at 45 CFR 46.110(c).

(12) HHS regulations at 45 CFR 46.110(b)(2) permit use of expedited procedures for review of minor changes to previously approved research. OHRP finds that the IRB has employed expedited procedures to review changes that exceed this limitation.

Corrective Actions: OHRP acknowledges that these matters of non-compliance (8-12) were identified by outside expert consultants hired by U. Penn. to review the IRB policies and procedures. OHRP notes that in response U. Penn. hired a new IRB director and implemented many of the changes recommended by the outside consultants. These include: (i) new procedures for the IRB including reporting to the IRB members via the agenda all actions taken by expedited review since the previous meeting and solicitation of comments; (ii) if any doubt exits regarding the appropriateness of expedited review, staff schedule review by the full IRB; (iii) all protocols are now assigned to a specific IRB for all aspects of initial and continuing review; (iv) all members now receive complete copies of the continuing review information; (v) all substantive emendments are now reviewed by the convened IRB; and (vi) additional education and training of IRB members, staff, and research investigators. OHRP finds that the corrective actions adequately address this finding and are appropriate under the U. Penn. Multiple Project Assurance.

D. Additional Concerns and Questions Regarding General Human Subjects Protections at U. Penn.

(13) HHS regulations at 45 CFR 46.116 require that the information provided in the informed consent documents be in language understandable to the subject. OHRP is concerned that some informed consent documents approved by the IRB appeared to include complex language that would not be understandable to all subjects.
Please respond.

(14) Continuing IRB review of research must be substantive and meaningful. In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including (a) the number of subjects accrued; (b) a description of

any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (c) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB (see OPRR Reports 95-01). Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

OHRP is concerned that continuing review of research by the IRB regularly failed to satisfy these requirements. In specific, the continuing review form did not solicit information regarding complaints or withdrawals or recent literature. Please respond.

(15) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk and not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. Additionally, where the convened IRB specifies conditions for approval of a protocol that are to be verified as being satisfied by the IRB Chair or another IRB member designated by the Chair, the approval period must begin on the date the protocol was reviewed by the convened IRB, not on the date the IRB Chair or his or her designee verifies that IRB-specified conditions for approval have been satisfied.

OHRP is concerned about numerous instances in which the IRB apparently failed to conduct continuing review of research at least once per year. For example, study number 3587 had initial review June 1, 1994, and continuing review August 18, 1995, and November 18, 1996; initial review of study number 2664 was on October 23, 1998, and there never was a continuing review (trial continued until at least January 2000); initial review for study number 1821 occurred May 9, 1994, continuing reviews September 14, 1995, January 21, 1997, December 16, 1997, and February 24, 1999. Please respond.

(16) U. Penn's March 10, 2000 Report of the Protection of Human Subjects Enrolled in Gene Therapy Research Conducted by the Institute of Human Gene Therapy at the University of Pennsylvania stated that an ad hoc internal committee, chaired by the Provost, is reviewing human subjects protections at U. Penn. and will make recommendations by "June 2000." Please provide OHRP a copy of this report.

E. Concerns and Questions Regarding the Following Specific Gene Therapy Projects

Research Project: "Treatment of Advanced CNS Malignancy with Recombinant Adenovirus H5.010RSVTK: Phase I Trial"

(17) OHRP is concerned that the informed consent documents reviewed and approved by the IRB for this study may have failed to adequately address the following element required by HHS regulations at 45 CFR Section 46.116(a)(1): an explanation of the purposes of the research. The title referred to this study as "treatment" although it was a phase I trial. In addition, the informed consent document stated "The purpose of this study is to determine the effectiveness and safety of a gene..." However, Phase I trials ordinarily are not designed to study effectiveness. Please respond.

Research Project: "Phase I Trial of AdRSVtk Virus with Ganciclovir in Patients with Unresectable Malignant Mesothelioma"

(18) OHRP is concerned that the informed consent documents reviewed and approved by the IRB for this study may have failed to adequately address the following element required by HHS regulations at 45 CFR Section 46.116(a)(2): An adequate description of the reasonably foreseeable risks and discomforts. The informed consent document approved by the IRB in September of 1997 stated "[w]e have already treated more than 15 patients with this virus without any serious side effects." However, a December 31, 1996 report to FDA stated "There have been two serious adverse events reported." Please respond.

Research Project: "Phase I clinical Trial Utiliting Gene Therapy for Limb Girdle Muscular Dystrophy..."

(19) OHRP is concerned that the informed consent documents reviewed and approved by the IRB for this study may have failed to adequately address the following element required by HHS regulations at 45 CFR 46.116(a)(1): A complete description of the procedures to be followed, and identification of any procedures which are experimental. The protocol included the development of immortalized white cell lines from subject's blood. This was not mentioned in the informed consent document. Please respond.

Research Project: "Treatment of Recurrent or Progressive Malignant Glioma with a Recombinant Adenovirus Expressing Human Interferon Beta"

(20) OHRP is concerned that when reviewing the protocol application, the IRB appeared to lack sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. Recruiting materials (sent to physicians) were not reviewed and approved by IRB when research was originally approved. The Research Nurse Coordinator sent these materials to the IRB five months

later for review and approval. Please respond.

(21) OHRP is concerned that the informed consent documents reviewed and approved by the IRB for this study may have failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(1): an explanation of the purposes of the research. The informed consent document stated "[t]he purpose of this research study is to determine the safety and effectiveness of a recombinant adenovirus when it is injected into brain tumors." Phase I trials ordinarily are not designed to test effectiveness.

(b) Section 46.116(a)(2): An adequate description of the reasonably foreseeable risks and discomforts. The risk description seems inadequate, particularly the risks of the LP (just stated "headache" among a list of other risks. The document did not state the likelihood or severity of the headache which might require a blood patch procedure to treat.)

Please respond.

Research Project: Gene Therapy of CF Lung Disease using a Third Generation Adenovirus: A Phase I Trial

(22) Department of Health and Human Services (HHS) regulations at 45 CFR 46.116 require that an investigator seek informed consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. OHRP is concerned that payment for participation instituted after the trial was underway may have represented undue influence to subjects. A June 10, 1997 letter from the Principle investigator to the Associate Director for Regulatory Affairs noted that "...we have experienced difficulty recruiting participants for this clinical trial." Sometime after that letter, payment for participation in the study was instituted at $1,550. OHRP is concerned that this level of compensation was instituted to influence subjects to participate who might otherwise have deemed the risks and discomforts to be too high. Please respond.

Please submit to OHRP your response to the above questions and concerns no later than July 2, 2001. If upon further review of the concerns and questions, U. Penn. identifies additional instances of non-compliance with the HHS regulations for protection of human subjects, please include detailed corrective action plans to address the noncompliance.

OHRP appreciates your institution's continued commitment to the protection of human research subjects. Do not hesitate to contact me if you have any questions regarding this matter.

Sincerely,

Kristina C. Borror, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Nicholas Kefalides, Chair, U. Penn. IRBs
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
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