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September 26, 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 Serman, 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) has reviewed your report of September 12, 2001, regarding the above referenced research conducted at University of Pennsylvania (U Penn).

Based upon its review, OHRP makes the following determinations.

A. Findings Regarding Research Project: “Recombinant Adenovirus Gene Transfer in Adults with Partial Ornithine Transcarbamylase Deficiency”

(1) OHRP finds that when reviewing protocol applications, the Institutional Review Board (IRB) often lacked sufficient information to make the determinations required for approval of research under Department of Health and Human Services (HHS) regulations at 45 CFR 46.111.

Corrective Action: OHRP acknowledges that U Penn has established Sponsor-Investigator Standard Operating Procedures (SOP) which require that any protocol amendment be prepared using a strike-out function to highlight changes and that each change must be outlined in a cover memo. OHRP also acknowledges that the U Penn IRB now has a written requirement that recruitment materials must be submitted to the IRB for review and approval. In addition, investigators will be provided with additional guidance on protocol drafting. OHRP also acknowledges that the Institute for Human Gene Therapy will no longer sponsor clinical trials, and all trials have stopped further enrollment.

(2) OHRP finds that the informed consent documents reviewed and approved by the IRB for the OTCD study 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.

Corrective Action: OHRP acknowledges that U Penn is instituting new SOPs detailing instructions to Sponsor-Investigators regarding informed consent documents, and specific IRB SOPs regarding general requirements and documentation of informed consent and assent. In addition, U Penn is currently training investigators, IRB members and IRB staff on these issues.

(3) HHS regulations at 45 CFR 46.109(a) require that the IRB review and approve all non-exempt human subject research. 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.” OHRP finds that this screening for prospective subjects involved human subjects research and occurred prior to IRB approval for this activity.

Corrective Action: OHRP acknowledges that the U Penn IRB reviewed information regarding the recruitment activities two months after the screening activity and that the IRB subsequently approved the informed consent document for this activity approximately one year later. OHRP also acknowledges that the IRB currently requires that new protocol submissions clearly identify the need for IRB review and approval of all information to be given to subjects as part of the recruiting process and that recruiting strategies themselves must be approved.

B. Findings Regarding U Penn’s System for Protecting Human Subjects

(4) 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 finds that some informed consent documents approved by the IRB appeared to include complex language that would not be understandable to all subjects.

Corrective Action: OHRP acknowledges that the IRB’s Guide to Daily Operations Manual has a suggested Glossary of Lay Language Terms which will be placed on the website to aid investigators in preparing and IRB members in reviewing informed consent documents.

(5) 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 finds numerous instances in which the IRB failed to conduct continuing review of research at least once per year.

Corrective Action: OHRP notes that the U Penn IRB has discontinued the practice of setting renewal dates based on the date of final approval and as of November 2000, all protocols are on a renewal cycle consistent with the guidance provided by OHRP.

C. Findings Regarding the Following Specific Gene Therapy Projects

Research Project: “Phase I Trial of AdRSVtk Virus with Ganciclovir in Patients with

Unresectable Malignant Mesothelioma”

(6) OHRP finds that the informed consent documents reviewed and approved by the IRB for this study 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.

Corrective Action: OHRP acknowledges that the IRB now pays particular attention to statements in the informed consent documents regarding prior subject experience to ensure that they are up-to date and correlate with the available clinical data.

Research Project: “Phase I clinical Trial Utilizing Gene Therapy for Limb Girdle Muscular Dystrophy...”

(7) OHRP finds that the informed consent documents reviewed and approved by the IRB for this study 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, but this was not described in the informed consent document.

Corrective Action: OHRP acknowledges that the IRB is aware that such cell line development must be discussed expressly and will be cognizant of it in future consents requiring such action.

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

(8) OHRP finds that the informed consent documents reviewed and approved by the IRB for this study failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116(a)(2): An adequate description of the reasonably foreseeable risks and discomforts. The risk description was inadequate, particularly the risks of the lumbar puncture.

Corrective Action: OHRP acknowledges that in the future the IRB will ensure that such risks are more explicitly described.

OHRP finds that the corrective actions referenced above adequately respond to OHRP’s findings and concerns. As a result of the above determinations, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

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. Borrer, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

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