DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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July 10, 2000

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RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1509

Research Projects: Molecular Mechanisms of HIV Neuropathogenesis (NS34293)
HIV-1, Monocytes and the Blood/Brain Barrier (NS36126)
Neuronal Electrophysiology in HIV Dementia (NS36127)
Principal Investigator: Dr. Howard Gendelman

Dear Drs. Maurer, Prentice, Burgher, and Belck:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks has reviewed the University of Nebraska Medical Center's (UNMC's) June 23, 2000 report regarding the above referenced research.

Based upon its review of UNMC's report, OHRP makes the following determinations:

(1) OHRP acknowledges your report that the UNMC has never conducted research involving fetal transplantation in human subjects. Based upon this information, OHRP finds that the requirements of Section III of Public Law 103-43 were not applicable to the above referenced research activities, nor any other research previously conducted by UNMC.

(2) OHRP acknowledges your report that research involving fetal tissue obtained form dead fetuses was conducted by UNMC in accordance with applicable state and local laws. Based upon this information, OHRP finds that the requirements of Department of Health and Human Services (HHS) regulations at 45 CFR 46.210 were satisfied for such fetal tissue research.

(3) OHRP finds no evidence that human subject research supported by the above referenced HHS awards was conducted without appropriate Institutional Review Board (IRB) review and approval.

As a result of the above findings, there should be no need for further OHRP involvement in this matter. Of course, OHRP must be notified should new information be identified which might alter the above determinations.

Furthermore, OHRP would like to provide the following additional guidance:

(1) Regarding IRB protocol # 162-93, OHRP notes that on June 14, 1993, the IRB approved an amendment to the protocol under which two HHS-funded grants were incorporated into the IRB-approved protocol. The IRB records provided to OHRP for protocol #162-93 did not appear to include copies of the actual grant applications.

OHRP reminds you that HHS regulations at 45 CFR 46.103(f) require that an institution with an approved assurance shall certify that each *application* for research has been reviewed and approved by the IRB (please see additional OHRP guidance at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/aplrev.htm, copy enclosed).

(2) Regarding the most recent version of the IRB-approved informed consent document for IRB protocol # 162-93, OHRP notes the following description of the purpose of the study:

> "The purpose of this study is to collect large numbers of . . .blood leukocytes form normal donors for various research studies in laboratories of the [UNMC]. The purposes of the research studies for which these normal donor cells may be used are: 1) to study the interactions between viruses and normal white cells to better understand how virus-infected cells cause disease and to develop new treatments to prevent disease; 2) to study different ways of processing and freezing normal human peripheral blood stem cells for infusion following high dose therapy to patients with otherwise incurable cancers."

(a) ORHP acknowledges that this general description of the purpose of the research appears to be accurate. However, when more specific purposes of the research activities using donor leukocytes are known, OHRP would recommend that such information be incorporated into the informed consent document (e.g.,

to learn about the effect of the AIDS virus on white cells; or to learn how the AIDS virus causes brain injury).

(b) Furthermore, it appears that blood leukocytes from normal donors sometimes are applied to experiments that also use fetal cells derived from dead fetuses. Since some subjects might object to participation in such research, OHRP recommends that the IRB assess whether additional information should be provided to subjects in the informed consent document regarding this aspect of the research so that their decision to participate is more fully informed.

(3) As you are aware, 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 (i) the number of subjects accrued; (ii) 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; (iii) 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 (iv) 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 at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc95-01.htm, copy enclosed). Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

(a) OHRP acknowledges that the continuing review applications used by the UNMC IRB include the above information and documents, and that separate actions and votes are documented in the minutes of IRB meetings for each protocol undergoing continuing review.

(b) The minutes of the November 18, 1999 meeting with respect to continuing review of research state that the "IRB administrative staff perform a pre-review of the applications for continuing review listed below including the complete protocol and informed consent/assent forms." Please be aware that "primary reviewers" referenced above in OHRP's guidelines for continuing review should be voting members of the IRB.

(c) Please note that, in accordance with HHS regulations at 45 CFR 46.115(a)(2), the minutes of IRB meetings should document for protocols undergoing continuing review (i) any changes or clarifications required by the IRB; and (ii) a written summary of any discussions of controverted issues and their resolution.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely

Michael A. Carome, M.D.
Chief, Compliance Oversight Branch
Division of Human Subject Protections

Enclosures: (1) OHRP guidance memorandum on review of grant applications
(2) OPRR Reports 95-01

cc with enclosures:
Dr. Howard Gendelman, University of Nebraska Medical Center
Dr. Bruce Gordon, Chair, IRB, University of Nebraska Medical Center

cc without enclosures:
Dr. John Mather, Director, Office of Research Compliance and Assurance, Department of Veterans Affairs
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. Melody H. Lin, OHRP
Dr. J. Thomas Puglisi, OHRP
Ms. Michele Russell-Einhorn, OHRP
Dr. Katherine Duncan, OHRP
Mr. George Gasparis, OHRP