DEPARTMENT OF HEALTH & HUMAN SERVICES

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Joyce Cashman
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RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1494

Research Project: Embryonic Dopamine Cell Implants for Parkinson's Disease: A Double Blind Study
Principal Investigator: Curt Freed, M.D.
UC Study Number: 93-097

Research Project: Embryonic Dopamine Cell Implants for Parkinson's Disease: Putamen and Substantia Nigra Grafts
Principal Investigator: Curt Freed, M.D.
UC Study Number: 95-143

Dear Dr. Shore and Ms. Cashman:

The Office for Human Research Protections (OHRP) has reviewed the University of Colorado Health Sciences Center's (CU's) report dated November 15, 2001 regarding the above-referenced research. Based on the review,

OHRP makes the following determinations:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.111(a)(1) and (a)(2) require that, in order to approve research, the Institutional Review Board (IRB) shall determine that risks to subjects are minimized and that risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. OHRP finds that the IRB did not ensure that risks to subjects were minimized when they approved protocol stopping rules that only related to adverse events related to surgery (30 days post-op.) These rules did not take into account delayed events due to the transplanted material itself that could have occurred at anytime after transplantation.

Corrective Action: OHRP acknowledges that the stopping rules have been revised to include worsening of Parkinsonism and evaluation of effectiveness.

(2) OHRP finds that the informed consent documents reviewed and approved by the IRB for these projects failed to adequately address the following element required by HHS regulations at 45 CFR 46.116(a)(2): a description of the reasonably foreseeable risks and discomforts. For example, the informed consent document approved by the IRB on July 8, 1997 stated that only 3 subjects had serious adverse events when 8 actually had, according to reports to the Performance Safety Monitoring Board (PSMB). In addition, a letter dated December 30, 1999 from the principal investigator to the PSMB stated "shortly after we started doing fetal cell transplants in 1988, we noted that transplants tended to increase the likelihood of drug-induced dyskinesias." However, this risk was not added to the informed consent document until May 17, 2001.

Corrective Action: OHRP acknowledges that subsequent versions of the informed consent document correctly noted the number of adverse events and the likelihood of dyskinesias.

(3) HHS regulations at 45 CFR 46.116 require that the information that is given to subjects must be in language understandable to the subject. OHRP finds that the informed consent document approved by the IRB for these projects appeared to include complex language that would not be understandable to all subjects. For example, the informed consent document approved by the IRB on June 3, 1998 for protocol # 93-097 had phrases such as labile hypertension, transient disturbance, and lacerating, which may not be understandable to subjects. The informed consent document approved by the IRB on July 8, 1997 also appeared to contain complex language (e.g., angina, occlusion, cardiac catheterization).

Corrective Action: OHRP acknowledges that the CU IRB has improved its standards for informed consent language and use of lay members, that protocol # 93-097 is closed to new enrollment and that it is unlikely that such language would not have been approved today. OHRP also acknowledges that the informed consent document for protocol # 95-143 does not appear to include complex language.

(4) OHRP finds that when reviewing the above-referenced protocol applications, the IRB 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) Protocol # 93-097 called for subjects to perform videotapings of their motor performance. Separate instructions were given to subjects describing how to do the recordings. The subjects were also asked to fill out daily diaries. There is no evidence that the IRB ever reviewed the instructions or survey.

(b) A quarterly report of protocol # 93-097 submitted to the PSMB December 31, 1997 referred to a "blindedness test" in which subjects were surveyed about whether or not they thought they received the transplant. There is no evidence that the IRB reviewed this instrument.

Corrective Action: OHRP acknowledges that these reviews were done prior to the 1999 suspension of human subjects research at CU, and that since the suspension, the CU IRB has required patient diaries, surveys and instructions to be submitted for IRB review prior to approval of a protocol.

(5) One of the reviewers on protocol # 93-097 on January 17, 1997 wanted the principal investigator to add a statement to the informed consent document to indicate that the investigators can withdraw the subject without their consent, and a signature line to indicate a subject's wishes to wait for the final results of the study before getting the transplant. In addition, on September 24, 1999 the IRB suggested some changes to the informed consent document for Protocol # 95-143, including listing the number of drill holes in the skull and describing immunosuppressant drugs as preventing your immune system from attacking the transplanted tissue. OHRP finds that these changes were not made to the protocol or informed consent document.

Corrective Action: OHRP acknowledges that these reviews were done prior to the 1999 suspension of human subjects research at CU. OHRP also acknowledges that the re-review of protocol # 93-097 after the suspension closed the protocol to new enrollment, and that the use of immunosuppressant drugs was added to the informed consent document for protocol #95-143. However, OHRP notes that the number of drill holes in the skull was never added to the informed consent document for that protocol. Please revise the informed consent document accordingly.

(6) OHRP finds that unanticipated problems involving risks to subjects or others were not reported to the IRB and/or OHRP as required by HHS regulations at 45 CFR 46.103(a) and (b)(5). In particular, OHRP notes that a letter from the IRB to Dr. Oliver dated January 23, 1994 stated that the IRB was not made aware of a death of a subject until the investigator requested a modified consent document with a new surgical approach.

Corrective Action: OHRP acknowledges that under CU IRB revised policies, failure to report a serious adverse event can result in the suspension of a protocol, and that reporting requirements have been reviewed with the investigator, who has since shown compliance with and understanding of the requirements.

(7) HHS regulations at 45 CFR 46.206 require that research involving fetal material be conducted in accord with any applicable Federal, State, or local laws or regulations regarding such activities. Federal Public Law 103-43 42 USC 289g-1 "Research on Transplantation of Fetal Tissue" requires that full disclosure be provided to the woman donating fetal tissue with regard to the attending physician's interest, if any, in the research to be conducted with the tissue, and any known medical risks to the woman or risks to her privacy that might be

associated with the donation of the tissue and that are in addition to risks of such type that are associated with the woman's medical care. The "Medical Director's Statement" includes statements that the Director's only research interest is the betterment of mankind and that there are no medical risks to the woman or her privacy that may be associated with the donation in addition to those associated with her medical care. Under the Federal law cited above, the attending physician must declare that this disclosure is made to the woman donating the tissue. OHRP finds, as UC acknowledged, that this statement was not provided to the donor, in contravention of Federal law and HHS regulations.

Corrective Action: OHRP acknowledges that attending physician's interest in the research, and any known medical or privacy risks to the woman that are in addition to risks associated with the woman's medical care will be added to the donor consent document. However, OHRP notes that CU plans to remove these statements from the medical director's statement. Please note that, under 42 USC 289g-1(b)(2)(c) the physician's statement must include a declaration that full disclosure has been provided to the woman with regard to the attending physician's interest, if any, in the research to be conducted with the tissue, and any known medical risks to the woman or risks to her privacy that might be associated with the donation of the tissue and that are in addition to risks of such type that are associated with the woman's medical care. Please ensure that such a statement remains in the medical director's statement.

OHRP finds that the above corrective actions are adequate and are appropriate under the CU MPA. As a result, 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 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,

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

cc: Ms. Elizabeth Hoffman, CU
Dr. Jay A. Gershen, CU
Dr. Richard D. Krugman, CU
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Dr. Christopher Kuni, Co-Chair Panel A
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Dr. Allan Prochazka, Co-Chair Panel B
Dr. Stephen Barlett, Co-Chair Panel B
Dr. Adam Rosenberg, Co-Chair Panel C
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