DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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October 30, 2001

Judy Matuk, M.S.
Associate Director, Office of Research Compliance
State University of New York at Stony Brook
Office of the Vice President for Research
Stony Brook, NY 11794-3368

RE: Human Research Subject Protections Under Federalwide Assurance FWA– 125

Research Project: Bone Marrow Transplantation and Anti-Tumor Effects of Interleukin II
P.I.: Dr. Amitabha Mazumder
Protocol Number: IND BB8229

Dear Ms. Matuk:

The Office for Human Research Protections (OHRP) has reviewed your report of October 16, 2001, regarding the above referenced research conducted at State University of New York at Stony Brook (SUNYSB).

Based upon its review, OHRP finds that the corrective actions noted below adequately address the findings made by OHRP in its August 29, 2001 letter.

(1) OHRP found that when reviewing this protocol application, the Committee on Research Involving Human Subjects (CORIHS), SUNYSB's Institutional Review Board (IRB), 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 CORIHS is sending a letter to the SUNYSB community to remind investigators of the information that must be provided to the IRB in order to ensure review and approval by the committee. OHRP also acknowledges that the IRB membership has doubled and two IRBs have been formed to allow adequate time for a more detailed, effective review of research.

(2) HHS regulations at 45 CFR 46.117(a) require that informed consent be documented by the use of a written consent form approved by the IRB. OHRP found that the first subject was consented with a previous version of the informed consent document, unbeknownst to the investigators. When the investigator learned this, the subject should have received the updated information.

Corrective Action: OHRP acknowledges that CORIHS is sending a letter to all investigators reminding them to use only current versions of informed consent documents and to provide additional information to subjects when it becomes available.

Based on SUNYSB's responses to questions and concerns in OHRP's August 29, 2001 letter, OHRP makes the following additional determinations regarding the above-referenced research project.

(3) HHS regulations at 45 CFR 46.107(a) require that the IRB have members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. OHRP finds that CORIHS did not appear to have an immunologist or oncologist for review of this protocol, and that there is no evidence of expert consultants in these areas. While Dr. Pearl is the oncologist on the IRB, he was unable to attend the meeting at which this protocol was initially reviewed and approved.

(4) OHRP finds that the informed consent documents reviewed and approved by the IRB for these projects did not adequately address the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(2): A description of the reasonably foreseeable risks and discomforts. The possibility of toxicity of the added cells was never mentioned in the informed consent document until November of 2000, even though a goal of the research was to study the toxicity of the added cells as early as April of 1999. OHRP acknowledges that no subject received tumor cell lysates.

(b) Section 46.116(a)(3): A description of any benefits to the subject or others that may *reasonably* be expected from the research. OHRP finds that the informed consent document approved by the IRB 12-1-98 overstated potential for

benefits: it stated that the infusion of immunized cells "will increase your immune response to the cancer." This was not known at the time.

(5) HHS regulations at 45 CFR 46.111(a)(1) stipulate that in order to approve research, the IRB shall determine, among other things, that risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk. For this research, appropriate testing of the peripheral blood stem cells (PBSCs) for microbiological contamination was an important procedure for minimizing risks to subjects. In a 1-19-01 response to concerns from the FDA, the investigators stated that mycoplasma and endotoxin testing had been and would be done on the cells. OHRP finds that endotoxin and mycoplasma testing were not performed on the PBSCs for each subject enrolled in the protocol.

Corrective Actions: OHRP acknowledges that the study was halted by the Vice President for Research with concurrence by the Director of SUNYSB's Cancer Center. In addition, SUNYSB has promulgated a policy requiring all cancer therapy protocols to be reviewed and approved for potential implementation by the Division Head of Neoplastic Diseases prior to consideration by the CORIHS. OHRP also acknowledges that the IRB chairs have determined that future transplant protocols submitted to the committees by Dr. Mazumder will be subject to short approval periods, frequent progress reports, and monitoring by the Division Head of Neoplastic Diseases.

OHRP has determined that these corrective actions appropriately address the additional findings and are appropriate under the SUNYSB FWA. 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 offers the following additional guidance regarding general human subjects protections at SUNYSB.

(6) The Application for Approval for Human Subjects Research solicits information on subject populations, including number of men, women, pregnant women, minorities, minors, and mentally handicapped. OHRP notes that other vulnerable populations mentioned in the regulations include economically or educationally disadvantaged persons (see HHS regulations 45 CFR 46.111(b)).

(7) OHRP notes that the institution should have written IRB policies and procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(a) and 103(b)(5): The procedures for ensuring prompt reporting to **OHRP** of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval.

(8) 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. HHS regulations at 45 CFR 46.108 require that review must be conducted by the convened IRB unless the protocol qualifies for expedited review. Regardless of what CORHIS is calling the "approval period," continuing review of a protocol not eligible for an expedited review procedure must occur within one year of the date of the last review by the convened IRB.

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. Robert Schneider
Dr. Amitabha Mazumder, SUNYSB
Dr. Harold Carlson, Chairperson, SUNYSB
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
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