DEPARTMENT OF HEALTH & HUMAN SERVICES

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August 29, 2001

Dr. Robert Schneider
Director of Informatics and Compliance
State University of New York at Stony Brook
Office of the Vice President for Research
Stony Brook, NY 11794-3365

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 Dr. Schneider:

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

Based upon its review, OHRP makes the following determinations regarding the above-referenced research:

(1) OHRP finds that when reviewing this protocol application, the Committee on Research Involving Human Subjects (CORIHS) 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. For example, when the IRB initially reviewed this project, they received only minimal information regarding (a) subject recruitment and enrollment procedures; (b) the origin of the tumor cell used for immunization of peripheral blood stem cells (PBSC); and (c) that the culture medium to be used in the immunization of PBSCs contained animal sera (fetal bovine and horse sera.) Even when the CORIHS was told that the medium contained animal serum on 11-20-00, it was only told it contained fetal bovine serum (FBS), not horse serum.

Action 1– Required: Please provide OHRP with a corrective action plan to ensure that this and other investigators provide sufficient information for the CORIHS to make the determinations required for approval of research. OHRP acknowledges that CORIHS is and will be asking in this and other studies that use FBS that no future subjects be enrolled until the consent form is revised to describe the theoretical possibility of contracting transmissible spongiform encephalopathies.

Action 2– Required:Please also provide OHRP with a list of subjects (code number only) and date of enrollment of any subjects enrolled after May of 2001.

(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 finds 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 will require the investigators to give subjects all updated information as approved by the IRB. Please provide OHRP with a corrective action plan outlining additional measures to ensure that all investigators use only current versions of informed consent documents and will provide additional information to subjects when it becomes available.

OHRP has the following additional concerns and questions 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 is concerned 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. Please respond.

(4) OHRP is concerned that the informed consent documents reviewed and approved by the IRB for these projects may not have adequately addressed the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(1): A complete description of the procedures to be followed, and identification of any procedures which are experimental: The informed consent document did not give any detail about how cells will be “immunized” by exposing a subject’s cells to cytokines and possibly autologous or allogeneic tumor cell lysates.

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

(i) Some of the side effects listed in the protocol were not mentioned or adequately described in the informed consent document– pulmonary edema was inadequately described as lung congestion and cerebrovascular disorders were not mentioned for IL-2 and hemorrhage was not mentioned for GM-CSF.

(ii) The possibility of toxicity of the added cells was never mentioned in the informed consent document until November of 2000, at which time it was not pointed out to the CORIHS.

(c) Section 46.116(a)(3): A description of any benefits to the subject or others that may *reasonably* be expected from the research. OHRP is concerned 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.

Please respond.

(5) HHS regulations at 45 CFR 46.110(b)(2) permit use of expedited procedures for review of minor changes to previously approved research. OHRP is concerned that the IRB has employed expedited procedures to review changes that appear to exceed this limitation. For example, on 4-13-99 the IRB reviewed and approved by expedited procedures an amendment to the protocol that included a "major change" in which the first 5 patients would receive PBSC cultured without tumor cell lysates to "provide a background for studying the toxicity of the added cells...." Please respond.

(6) HHS regulations at 45 CFR 46.111(a)(1)(i) state 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. OHRP has the following concerns regarding risks in this protocol:

(a) The protocol initially approved by the CORIHS stated that tumor cells would be lysed by freeze-thaw and then separated by centrifugation and filtration to remove whole cells. In April of 1999, the protocol changed to sonication, with no filtration. It is not clear why this change was made as it appears to increase the chance of contamination by infectious agents and whole tumor cells. Please respond.

(b) The CORIHS had concerns during its continuing review on 12-14-00, including the inclusion of FBS, safe injection of cells into subjects, and toxicity testing in animals. OHRP can not find evidence that the principal investigator ever addressed the animal testing issue. Please respond.

(c) The protocol that underwent continuing review on 12-14-00 contained a major change in which the study was open to different types of cancer besides stage IV breast cancer (including head and neck cancer, ovarian cancer, sarcoma, adenocarcinoma and leukemia.) However, the power calculations for the protocol did not change, and the investigators used the same survival statistics from metastatic breast cancer but only took out the word "breast" from the Statistical Considerations section of the protocol. Please respond.

(d) In a 1-19-01 response to concerns from the FDA, the investigators stated that the "minimum viability" of PBSCS would be 70%, and that other testing had been and would be done on the cells. Please provide OHRP with cell viability endotoxin assay, cytotoxicity/tumor detection assay, mycoplasma testing, and CFU assay lab test results for PBSCs for each subject enrolled in the protocol.

(7) OHRP is concerned that the continuing review application for 1999 did not appear to include a summary of the human subjects aspects of this protocol for the previous year. Please respond.

(8) During the November 2000 continuing review, the IRB required some changes to the informed consent document. It is not clear that all the changes were made before final approval (e.g. simplify "hematuria," "alopecia," "exacerbation," "eosinophilia.")

OHRP has the following concerns and questions about the following additional research projects and general human subjects protections at SUNYSB.

(9) HHS regulations at 45 CFR 46.116(d) require that the IRB find and document four specific criteria when approving waiver or alteration of some or all of the required elements of informed consent. HHS regulations at 45 CFR 46.117(c) require specific findings on the part of the IRB for waiver of the usual requirements for the investigator to obtain a signed consent form from all subjects. Project #983387 (Principal Investigator: Gerard Brogan) involved an "anonymous consent form to obtained inferred consent." There is no indication that the IRB made the findings required to waive informed consent or documentation of informed consent. On 12-14-00, the IRB approved protocol # 20004088 (Principal Investigator: John Innis) and recommended that documentation of consent be waived. OHRP notes that, in accordance with 45 CFR 46.117(c)(1) that each subject should be asked if he or she want documentation linking him or herself with the research. Please respond.

(10) At the 12-14-00 meeting of the IRB, protocol # 2000-3920, the IRB stated that only adverse events that occur at an incidence greater than 1% should be added to the informed consent document. OHRP is concerned that it may be reasonable to include a description of additional risks, if foreseeable, even if the expected incidence is less than 1% (e.g., death or permanent disability). Please respond.

(11) 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. Information on no other vulnerable populations is solicited. Please respond.

(12) The Application for Exempt Category Review should make it clear that the exemption applies only to research in which the only involvement of human subjects will be in one or more of the listed categories. Please respond.

(13) OHRP is concerned that the institution does not have written IRB policies and procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(b)(4) and (5):

> (a) The procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.
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> (b) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and Department or Agency head 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.

Please respond.

OHRP would like to provide the following additional guidance.

(14) 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.

If the IRB does not re-approve the research by the specified expiration date, subject accrual should be suspended pending re-approval of the research by the IRB. (Enrollment of new subjects cannot ordinarily occur after the expiration of IRB approval. Continuation of research interventions or interactions in already enrolled subjects should only continue when the IRB finds that it is in the best interests of individual subjects to do so. OHRP and IRBs must address on a case-by-case basis those rare instances where failure to enroll would seriously jeopardize the safety or well-being of an individual **prospective** subject.)

Please submit to OHRP your response to the above required actions, questions and concerns no later than October 5, 2001. If upon further review of the concerns and questions, SUNYSB identifies 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. Amitabha Mazumder, SUNYSB
Dr. Harold Carlson, Chairperson, SUNYSB
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
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Mr. Barry Bowman, OHRP