DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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January 22, 2002

Michael Rosenblatt, M.D.
President
Beth Israel Deaconess Medical Center
330 Brookline Avenue
Boston, MA 02215

RE: Human Research Subject Protections Under the Multiple Project Assurance (MPA) M-1544

Research Project: A Phase I Study T Cells Modified with Chimeric antiCEA Immunoglobulin-T Cell Receptors (IgTCR) in Adenocarcinoma
Project Number: 94-1101-148
Principal Investigator: R.P. Junghans, M.D., Ph.D.

Research Project: A Phase I Study T Cells Modified with Chimeric antiGD3 Immunoglobulin-T Cell Receptors (IgTCR) in Metastatic Malignant Melanoma
Project Number: 94-1101-147
Principal Investigator: R.P. Junghans, M.D., Ph.D.

Dear Dr. Rosenblatt:

The Office for Human Research Protections (OHRP) has reviewed the Beth Israel Deaconess Medical Center (BIDMC) March 29, 2000 report regarding the above referenced matter. OHRP apologizes for the delay in responding to your report.

Based upon its review of your report, OHRP makes the following determination:

(1) OHRP finds that the following suspension of Institutional Review Board (IRB) approval was not reported to OHRP as required by Department of Health and Human Services (HHS)

regulations at 45 CFR 46.103(a) and 46.103(b)(5): the suspension of protocol #94-1101-148 by the General Clinical Research Center (GCRC) and the IRB in response to concerns from the GCRC nursing staff.

Corrective Action: OHRP acknowledges BIDMC's statement that the IRB administrators have been reminded about the reporting requirements and will assure that appropriate reporting is being carried out. However, OHRP has concerns about the adequacy of the written policies and procedures of the BIDMC IRB, as expressed below.

OHRP has the following concerns and questions regarding the above-referenced research:

(2) OHRP is concerned that the informed consent documents reviewed and approved by the IRB for protocol #94-1101-148 failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116 (a):

(a) Sections 46.116(a)(1) and (3): an explanation of the purposes of the research and a description of any benefits to the subjects or others which may *reasonably* be expected from the research. The main objectives of the study were to determine the safety and tolerability of the modified T-cells and to describe the pharmacokenetics of the T-cells. "Preliminary evaluation of efficacy" was a secondary objective. However, the informed consent document stated that "treatment on this research study may be helpful for controlling my disease" and that the study "will measure the effects of an immune therapy to fight the cancer cells in my body." The informed consent document does not clearly and explicitly state the primary purpose of the research (i.e., safety and tolerability of the modified T-cells). In addition, OHRP is concerned that the informed consent document refers to the intervention as "therapy" and "treatment," which may mislead the subjects about the potential for any benefit that could reasonably be expected from the research.

(b) Section 46.116(a)(2): A description of the reasonably foreseeable risks and discomforts. The following risks and discomforts were not adequately addressed in the informed consent documents:

(i) Risks of the placement of a central venous catheter (including pneumothorax, catheter sepsis, and arrhymia)

(ii) Risks of the treatment, particularly IL-2, to the heart. A subject, HF, had atrial fibrillation/flutter several hours after receiving a dose and died within days after receiving the fifth dose. This was deemed "possibly related" to the gene transfer, according to an August 12, 1999 letter from the principle investigator to the FDA. These risks were not added to the informed consent document. In addition, the informed consent document did not mention tachycardia, which

was listed in the protocol. A separate informed consent document for echocardiography was added at some point, which listed some possible heart risks of IL-2 treatment, but an August 9, 1999 amendment stated "the echocardiography consent will not be used henceforth." A September 20, 1999 submission for scientific review finally included rise in heart rate as a risk, but no other heart risks. An August 9, 1999 request for amendment indicated that "three adverse events of a cardiac nature" had been experienced by subjects: atrial flutter/fibrillation, cardiac sudden death, and supraventricular tachycardia (SVT). The informed consent document was not changed to reflect these events.

(iii) The informed consent document for protocol #94-1101-147 and #94-1101-148 stated "animals have been tested with this therapy and suffered no ill effects, but this may not reflect the toxicities that may be observed in humans." It is not clear that this particular vector system was tested in animals prior to human trials, as the statement in the informed consent document implies. The June 26, 1997 grant application to NIH stated that previous animal research studied "IgTCR-modified T cells" and "T cells with chimeric signaling molecules." OHRP can find no evidence that these were the same vectors that the principle investigator proposed to use. This data was published in 1995 and 1995, but publication of the production of the CEA IgTCR vector did not occur until 1999. The application also noted that no animal studies would be performed prior to clinical application in humans. The minutes of the December 5, 1994 IRB meeting stated "Dr. Junghans noted that there were no plans to test this protocol on animals because the data were too difficult to adapt to humans. There has been one animal study done with minimal data...."

Please respond. In your response to (b)(iii) above, please provide OHRP with copies of relevant articles describing the data referenced in the informed consent document and the December 5, 1994 IRB minutes.

(3) OHRP is concerned that the following unanticipated problems involving risks to subjects or others were not reported to OHRP as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5): An August 9, 1999 request for amendment indicated that "three adverse events of a cardiac nature" had been experienced by subjects: atrial flutter/fibrillation, cardiac sudden death, and SVT. These would not appear to be expected since the protocol and informed consent document did not mention them, and the principle investigator stated that the events were "possibly" or "probably" related to the research. Please respond.

(4) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent

immediate hazards to the subjects. OHRP is concerned that for protocol #94-1101-148 the investigator deviated from the IRB-approved protocol. The protocol exclusion criteria included significant cardiovascular disease. A subject, HF, had atrial fibrillation/flutter several hours after receiving a dose and died within days after receiving the fifth dose. This subject had "pre-existing coronary artery disease" according to the June 25, 1999 report of this incident. A March 7, 1999 letter from the principle investigator to FDA stated that the subject HF had "significant cardiac history, including a prior MI several years ago, and more recently atrial fibrillation...." OHRP is concerned that, according to the IRB-approved protocol, this subject should have been excluded from the study. Please respond.

(5) HHS regulations at 45 CFR 46.116 require that informed consent information be in language understandable to the subject or the subject's legally authorized representative. OHRP is concerned that the informed consent document approved by the IRB for these studies appeared to include complex language that would not be understandable to all subjects. For example, the documents included terminology such as "bowel dysfunction," "hemorrhage," "gastrointestinal tract," "administered," "toxicities," "oliguria," and "malaise." Please respond.

(6) In accordance with HHS regulations at 45 CFR 46.103(b) and 46.109(a), the IRB must review and approve all non-exempt human subject research covered by an assurance. The grant application for this research submitted to the Department of Defense stated that there would be "wet runs" with a volunteer donor. There was no mention of these "wet runs" in the IRB-approved protocol. Please respond. In your response, please provide a detailed description of the "wet runs" and clarify whether or not the IRB reviewed and approved these activities.

(7) A February 5, 1996 memo from the IRB to the principle investigator stated "you are asked to return to the IRB with in vitro efficacy and safety data and a final version of the clinical trials protocol prior to activation." It is not clear when activation occurred, or when the IRB received this data and the revised protocol. Please clarify and provide documentation of this data and re-review.

(8) HHS regulations at 45 CFR 46.110(b)(2) permit use of expedited procedures for review of minor changes to previously approved research during the period for which approval is authorized. On July 7, 1998, the principle investigator requested an amendment to the protocol that added a study arm and a new objective for the study ("determine whether IL2 changes the safety profile of the modified T cells.") The chair of the committee, R. Armour Forse, approved this amendment in an expedited manner on July 7, 1998. OHRP is concerned that this change appears to exceed the limits of minor and should have been reviewed by the convened IRB. Indeed, the IRB appears to have reviewed and approved this amendment at the convened September 8, 1998 meeting. However, two subjects were enrolled under the new protocol between July 7, 1998 (date of the expedited review) and September 8, 1998 (date of review by convened IRB), one on July 21, 1998 and one on August 20, 1998. Please

respond.

(9) On April 12, 1999, the principle investigator requested an amendment to the protocol to change the 4 doses to one dose, with a second dose at the discretion of the investigator. The informed consent documents submitted with this amendment still listed the original 4 doses, but the Chair, who reviewed this amendment in an expedited manner stated "the revised informed consent submitted was satisfactory." This change was made in a September 20, 1999 submission for scientific review. OHRP is concerned that one subject was enrolled between March 1, 1999 and January 12, 2000, prior to the change in the informed consent document. Please respond.

(10) An August 2, 1999 letter from Susan Greenspan, Program Director of the GCRC, to Alan Lisbon, IRB chair, stated that the protocol had been re-reviewed by the GCRC's Scientific Advisory Committee due to some concerns by the nursing staff. The protocol was placed on hold and it was recommended that a Data and Safety Monitoring Board (DSMB) be established to evaluate the protocol and related safety concerns. HHS regulations at 45 CFR 46.111(a) state that, in order to approve research covered by the regulations, the IRB shall determine that certain requirements are satisfied. OHRP is concerned that for this research the IRB may have failed to determine that the research plan made adequate provision for monitoring the data collected to ensure the safety of subjects, in accordance with HHS regulations at 45 CFR 46.111(a)(6). Please respond.

(11) On November 18, 1994 Susan Landsman, IRB Administrator, requested appropriate changes to the informed consent document for protocol #94-1101-147. Many of these changes were never made to the informed consent document, such as a more candid statement of the purpose of the research, and suggesting to the subject that they tell their doctor that they received this antibody, since it may cause problems with mouse antibody therapy in the future. Please respond.

(12) Written IRB policies and procedures should provide the operational details for each of the following procedures required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(4) and (5):

> (i) The procedures which the IRB will follow for conducting its initial review of research.
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> (ii) The procedures which the IRB will follow for conducting its continuing review of research.
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> (iii) The procedures which the IRB will follow for reporting its findings and actions to the institution.

(iv) The procedures which the IRB will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.

(v) The procedures which the IRB will follow 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.

(vi) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any Department or Agency head, and OHRP of (a) any unanticipated problems involving risks to subjects or others; (b) any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval.

OHRP is concerned that the Policies and Procedures in your report appear to lack operational details for these procedures. Please respond. In your response, please provide OHRP with any updated policies and procedures (see enclosed Guidance for Formulating Written IRB Policies and Procedures.)

Please provide your response to the above determinations and concerns so that OHRP receives it no later than March 5, 2002. If upon further review of the concerns and questions, BIDMC 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 the commitment of your institution to the protection of human 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 Dr. Alan Lisbon, Chair, BIDMC IRBs
Dr. Richard Junghans, BIDMC
Dr. Greg Koski, OHRP
Dr. Melody Lin, OHRP

Dr. Michael Carome, OHRP
Mr. George Gasparis, OHRP
Ms. Yvonne Higgins, OHRP
Mr. Barry Bowman, OHRP
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA