DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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May 9, 2002

Paul Levy
President
Beth Israel Deaconess Medical Center
330 Brookline Avenue
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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 Mr. Levy:

The Office for Human Research Protections (OHRP) has reviewed the Beth Israel Deaconess Medical Center (BIDMC) April 29, 2002 report regarding the above referenced matter.

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

(1) OHRP finds 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 informed consent document did not clearly and explicitly state one of the purposes of the research (i.e., to determine the 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 have misled 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) Risk of the interventions, particularly IL-2 administration (including tachycardia).

Furthermore, 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." This particular vector system was not tested in animals prior to human trials, as the statement in the informed consent document implies. OHRP notes that there was no appropriate animal model for this particular vector. However, it appears that it would have been appropriate to state " "animals have been tested with a similar vector and suffered no ill effects...."

Corrective Actions: OHRP acknowledges that many revisions have been made to the informed consent document and that the IRB is still reviewing the document. In addition, IRB staff and members have been educated about adhering strictly to all rules and regulations governing the review of human subject research.

(2) OHRP finds 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.

Corrective Actions: OHRP acknowledges that IRB administrators at BIDMC have been educated about all reporting requirements to ensure that any such events will be reported to OHRP. In addition, a new Policy and Procedure Manual has been drafted. However, OHRP recommends below that the BIDMC expand the procedures to include more operational details. For example, OHRP recommends that the procedures include a description of which office(s) or institutional official(s) is responsible for promptly reporting such events and a description of the required time frame for accomplishing the reporting requirements.

(3) 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 finds 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."

Corrective Actions: OHRP acknowledges that Dr. Junghans has submitted a revised informed consent document, which is currently under review by the IRB, that includes language that is more understandable to the subject.

(4) OHRP finds that when reviewing this protocol application, the IRB appeared to lack sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. 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." The IRB apparently did not review this data prior to activating the protocol.

Corrective Actions: OHRP acknowledges that the IRB will review this data prior to re-activating the protocol.

(5) 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, Dr. Armour Forse, approved this amendment in an expedited manner on July 7, 1998. OHRP finds that this change appears to exceed the limits of minor and should have been reviewed by the convened IRB. Although the IRB reviewed and approved this amendment at the convened September 8, 1998 meeting, two subjects were enrolled under the revised 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.

Corrective Actions: OHRP acknowledges that, had the amendment been submitted under

current IRB policies and procedures, it would have been automatically submitted to the convened IRB for review.

(6) 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.

Corrective Actions: OHRP acknowledges that further modifications have been required prior to activation of this study, and that the IRB staff reviews each specific change made to the informed consent document by the investigator in response to the IRB's requirements to ensure that the revisions were made before activating any protocol.

OHRP finds that the above corrective actions adequately address the above-referenced findings and are appropriate under the BIDMC MPA.

OHRP acknowledges that upon review of the above-referenced concerns, BIDMC has identified additional instances of non-compliance. These findings include study interventions occurring after expiration of IRB approval, failure to report this serious non-compliance to the appropriate Federal agencies, and failure of an investigator to obtain IRB review and approval prior to implementing changes to research, and to provide the IRB with sufficient information to make the required findings at 45 CFR 46.111. Your report and corrective actions appear to be adequate and appropriate under the BIDMC MPA. However, OHRP notes that one of the instances of non-compliance was reported to OHRP on the phone; such reports should be made in writing to the Division of Compliance Oversight.

OHPR has the following additional concern:

(7) 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.

OHRP acknowledges that an outside consultant has reviewed these activities. However, it is not clear whether or not these activities are human subject research. If so, the activities need to be reviewed and approved by the IRB. Please respond. In your response please indicate whether or not samples for the "wet runs" were obtained from volunteers for this purpose (as opposed to being clinically indicated), or if "wet run" samples were associated with private, identifiable information.

At this time, OHRP provides the following additional guidance:

(8) The BIDMC written IRB policies and procedures should be expanded to provide the operational details for each of the procedures required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(4) and (5), as noted in OHRP's April 30, 2002 letter to BIDMC. For further guidance on written IRB procedures, see our website at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/wirbproc.pdf

Please provide your response to the above concern so that OHRP receives it no later than June 10, 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
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Mr. Barry Bowman, OHRP
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Dr. David Lepay, FDA