DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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January 10, 2002

James W. Patrick, Ph.D.
Vice President and Dean of Research
Baylor College of Medicine
One Baylor Plaza, S103
Houston, Texas 77030

RE: Human Research Subject Protections Under Federal Wide Assurance (FWA) FW-0286
Research Projects: Gene Therapy Research Involving Adenoviral IL-2 Vector Conducted Under IND 7322 and IND 8243
Principal Investigator: Dr. Malcolm Brenner

Dear Dr. Patrick:

The Office for Human Research Protections (OHRP), formerly the Office of Protection from Research Risks (OPRR), has reviewed Baylor College of Medicine's (BCM) February 24, 2000 report and letter regarding the above-referenced research.

Based upon its review, OHRP notes the following:

(1) On January 18, 2000, Dr. Malcolm Brenner was notified by another institution that a seed stock adenoviral vector encoding interleukin 2 (IL-2) that did not receive proper testing was inadvertently used by that other institution to generate a tumor vaccine administered to two patients with neuroblastoma, and subsequent testing of the vector used in preparation of the vaccine had, in preliminary tests, tested positive by PCR for HIV and hepatitis C virus.

(2) Documentation provided to OHRP indicated that BCM used an adenoviral vector encoding the IL-2 gene that was originally derived from the same viral seed stock used at the other institution; however, the vector used by BCM had passed tests for safety, purity and identity before it was used to prepare tumor vaccines in cell culture. An algorithm provided by BCM to OHRP outlined the derivation of BCM Batch 7 and Batch 8, the batches used to derive the tumor vaccine administered to subjects at BCM. This algorithm indicated that Batch 7 tested negative for infectious agents both at the other institution and subsequently at BCM. Cells from Batch 7 were later used to create the BCM viral seed stock. This material also tested negative for infectious agents and was used to prepare Batch 8.

(3) BCM subsequently performed additional testing of its adenoviral vector tumor vaccine, with these results negative for contamination by HIV or hepatitis C virus.

Based upon the above information, OHRP finds no evidence of noncompliance with Department of Health and Human Services regulations at 45 CFR Part 46, particularly with respect to those provisions related to the reporting of unanticipated problems involving risks to subjects or others. 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.

At this time, OHRP offers the following additional recommendations regarding the informed consent documents for the above mentioned research:

(1) The informed consent documents did not mention the potential risk for autoimmune disease, although a publication coauthored by Dr. Brenner (Roskrow et al. Autoimmune Disease Induced by Dendritic Cell Immunization Against Leukemia. *Leukemia Research*.1999;23:549-557) indicated that in a mouse model, autoimmune disease was induced by dendritic cell immunization using a retroviral vector expressing IL-2. OHRP recommends that the BCM IRB consider whether it would be appropriate for the informed consent document to be revised to include the potential risk for autoimmune disorders, if this has not already been done.

(2) HHS regulations at 45 CFR 46.116(a)(1) require that informed consent documents include the expected duration of the subject's participation. The informed consent document for Study H6442: "Phase I Study of Chemokine and Cytokine Gene Modified Autologous Neuroblastoma Cells for Treatment of Relapsed/Refractory Neuroblastoma Using an Adenoviral Vector" indicated under item 3 (Purpose of the Study) that the subject's participation in this study "will last for a year"; however, under item 4 (Procedures), the document stated that "blood draws will need to be repeated once a month for a year, and then

once a year for **ten years** [emphasis added]." OHRP recommends that the BCM IRB consider whether the informed consent document should be revised to more clearly and consistently reflect the expected duration of participation, if this has not already been done.

(3) HHS regulations at 45 CFR 46.116(a)(2) require that informed consent documents include a description of the reasonably foreseeable risks and discomforts. OHRP notes the following discrepancies between the risks described in the study protocols and those described in the informed consent documents:

(a) The protocol for Study H6442, "Phase I Study of Chemokine and Cytokine Gene Modified Autologous Neuroblastoma Cells for Treatment of Relapsed/Refractory Neuroblastoma Using an Adenoviral Vector", provided to OHRP included the possible risk that the vaccine may cause tumors, although this risk was not mentioned in the informed consent document.

(b) The protocol for Study H6408, "Treatment of High Risk Leukemia with IL-2 Gene Modified Skin Fibroblasts and Autologous Tumor Cells", included the possibility of liver or renal dysfunction and the development of neurologic changes, although these risks were not mentioned in the informed consent document.

OHRP recommends that the BCM IRB consider whether the informed consent documents for studies H6442 and H6408 should be revised to include the above referenced risks, if this has not already been done.

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,

Leslie K. Ball, M.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Ralph Feigin, President, Baylor College of Medicine
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