DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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February 26, 2002

I. Dodd Wilson, M.D.
Chancellor
University of Arkansas for Medical Sciences
4301 West Markham Street, Slot 541
Little Rock, Arkansas 72206

RE: Human Research Subject Protections Under Federalwide Assurance 1119 and Multiple Project Assurance M-1451

Research Project: Phase II Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin 7) as an Immunotherapeutic Agent in Patients with Stage III or IV Melanoma with no Treatment Alternatives
IRB Protocol Number: 98-029
Principal Investigator: Laura F. Hutchins, M.D.

Dear Dr. Wilson:

The Office for Human Research Protections (OHRP) has reviewed the August 4, 2000 report from the University of Arkansas for Medical Sciences (UAMS) responding to concerns about possible noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR Part 46) that were presented in OHRP's May 22, 2000 letter regarding the above-referenced research.

The possible noncompliance involved the following:

> Possible failure to ensure prompt reporting of an unanticipated problem involving risks to subjects or others to the UAMS Institutional Review Board (IRB), appropriate institutional officials, and OHRP, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

Based upon its review of your report, OHRP finds no evidence of noncompliance with the HHS regulatory requirements for reporting unanticipated problems involving risks to subjects or others with respect to the above-referenced research. In particular, OHRP acknowledges the finding in your report that the death of a subject 22104 was most likely related to progression of the subject's underlying metastatic melanoma and not to the interventions under the above-referenced research protocol.

OHRP acknowledges your report that the principal investigator for the above-referenced research failed to comply with the UAMS policy regarding reporting of subject deaths to the UAMS IRB. Furthermore, OHRP acknowledges that UAMS has taken appropriate corrective action to address this deficiency including implementation of an appropriate education program regarding adverse event reporting requirements for the principal investigator and study coordinators involved in the conduct of the above-referenced research.

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 provides the following additional guidance:

> In accordance with HHS regulations at 45 CFR 46.103(b)(4), no change in approved research, during the period for which IRB approval has already been given, may be initiated without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the subjects.
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> OHRP noted at least two instances where the principal investigator for the above-referenced research protocol requested and obtained approval from the study sponsor to enroll subjects who did not satisfy the inclusion and exclusion criteria stipulated by the IRB-approved protocol. It is unclear from the UAMS IRB records whether the principal investigator sought and obtained approval from the UAMS IRB prior to the implementation of these protocol changes.
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> Please note that all protocol changes, including alterations of the inclusion and exclusion criteria stipulated by the IRB-approved protocol, must be approved by the IRB prior to the implementation of the changes by the investigators. Under HHS regulations at 45 CFR 46.110(b)(2), changes to the inclusion or exclusion criteria that are considered to involve a minor change to the research protocol may be approved by the IRB under an expedited review procedure.

OHRP appreciates the commitment of UAMS to the protection of human subjects. Please contact me if you have any questions regarding this matter.

Sincerely,

Michael A. Carome, M.D.
Director, Division of Compliance Oversight
Office for Human Research Protections

cc: Ms. Alma F. Pattillo, IRB Administrative Director, UAMS
Dr. Paul Gubbins, Chair, IRB-01 and IRB-02, UAMS
Dr. Marisue Cody, Chair, IRB-03, UAMS
Dr. Laura F. Hutchins, UAMS
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. John Mather, Director, Office of Research Compliance and Assurance
Veterans Health Administration
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. Jeffrey Cohen, OHRP
Mr. George Gasparis, OHRP
Ms. Freda Yoder, OHRP
Mr. Barry Bowman, OHRP