DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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July 1, 2004

Lee Hartwell, Ph.D.
President and Director
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue, No. D1-060
P.O. Box 19024
Seattle, WA 98109-1024

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1008 and Federalwide Assurance (FWA) 00001920

Research Project:	**Prevention of GVHD by In Vitro Deletion of Donor Cells with Monoclonal Anti-T Cell Antibodies and Complement Oncology Protocol 126**
Principal Investigator:	**Dr. Paul Martin**
Research Project:	**Autologous Transplantation for Patients with High Risk Stage II-III and Metastatic Breast Cancer Using a Conditioning Regimen of Busulfan and Cyclophosphamide and anti-TNF-a Therapy Oncology Protocol 681**
Principal Investigator:	**Dr. William Bensinger**

Dear Dr. Hartwell:

The Office for Human Research Protections (OHRP) has reviewed the Fred Hutchinson Cancer Research Center's (FHCRC) April 29, 2004 report, which was submitted in response to OHRP's letter of January 5, 2004 regarding the above-referenced research.

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

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.111 require the institutional review board (IRB) to make certain determinations in order to approve research, including (i) that risks to subjects are minimized, and (ii) that risks to subjects are reasonable in relation to the anticipated benefits, if any, to the subjects. OHRP finds that the principal investigator for Protocol 681 failed to provide accurate information to the IRB regarding the number of subjects enrolled, which was necessary for the IRB to make the determinations required by 45 CFR 46.111.

Corrective Action: OHRP acknowledges that FHCRC's current procedures include verification of information submitted by investigators by the FHCRC Protocol Office, with the IRB being informed of any discrepancies. In addition, the FHCRC Protocol and Data Monitoring Committee reviews all ongoing clinical trials annually.

(2) 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 notes that final approval of Protocol 126.3 was granted on June 21, 1985. One subject was enrolled in this protocol on June 6, 1985 and received a bone-marrow transplant on June 17, 1985. OHRP finds that the initiation of Protocol 126.3 was implemented prior to IRB approval.

Corrective Action: FHCRC has in place written procedures that require investigators to submit all changes in research to the IRB prior to their implementation. FHCRC procedures indicate that investigators will be notified in writing when their studies will be reviewed, and will be reminded that changes may not be implemented until final approval has been granted.

(3) 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. OHRP finds that the FHCRC IRB employed expedited procedures to review the following changes that exceed this limitation:

(a) The use of post-transplantation methotrexate in Protocol 126.2.

(b) The administration of a test dose of busulfan for purposes of determining pharmacokinetics for Protocol 681.

Corrective Action: OHRP acknowledges that FHCRC has changed its IRB manual to include a detailed checklist to assist its IRB chairs in determining when proposed protocol amendments represent a minor change to the research.

(4) HHS regulations at 45 CFR 46.116(a)(1) require that informed consent include a description of the procedures to be followed and identification of any procedures which

are experimental. OHRP notes that the informed consent document signed by one subject enrolled in Protocol 681 included the statement, "Either drugs [*sic*] [pentoxifylline or ciprofloxacin] may be given through your Hickman catheter if your physician thinks you may not be absorbing the medicine when you take it by mouth," although the intravenous form of pentoxifylline was not available at the time of the subject's enrollment. As a result, OHRP finds that the informed consent document signed by the above-referenced subject failed to meet the requirements under HHS regulations at 45 CFR 46.116(a)(1).

Corrective Action: OHRP acknowledges that FHCRC has subsequently utilized an electronic system to ensure that informed consent documents for all subjects are the most recent version available.

(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 finds that some of the language included in the informed consent document for Protocol 681 included language which would not be understandable to all subjects. For example, the IRB-approved informed consent document stated the following:

> (a) "If your marrow is treated to select stem cells, it will be incubated with the monoclonal antibody 12.8, which comes from mice and reacts with stem cells. The marrow is then passed over a column containing the protein avidin, which will bind these antibody-labeled stem cells."
>
> (b) "... this treatment regimen will also include the drug recombinant human granulocyte macrophage-colony stimulating factor or rhGM-CSF. Results from the use of rhGM-CSF in human trials (over 1000 cases) suggest the [*sic*] rhGM-CSF is well tolerated and may shorten engraftment time by stimulating white blood cell growth."
>
> (c) "Blood samples must be drawn at frequent intervals to follow the treatment and to monitor the return of marrow function. Granulocyte, platelet and red cell transfusions will be given as necessary to maintain adequate levels."

OHRP understands that FHCRC utilizes a family conference as part of its informed consent process. However, the format of these conferences and the information provided to the subject at that time were not described in the IRB-approved protocol. The information provided to subjects or their legally authorized representatives in the informed consent document may be particularly useful to subjects when finalizing their decisions regarding research participation in the absence of the investigators.

Corrective Action: OHRP acknowledges FHCRC's statement that certain parts of the informed consent document may be worded differently today. FHCRC has provided guidance to its investigators in an effort to make informed consent documents more

readable. The FHCRC IRB has established an informed consent subcommittee to evaluate issues relating to informed consent document readability and development of model documents.

(6) It was alleged that the FHCRC IRB failed to ensure that prospective subjects were adequately informed of the reasonably foreseeable risks and discomforts of the research, as required by HHS regulations at 45 CFR 46.116(a)(2). Based on materials submitted by the FHCRC in its previous reports, OHRP is unable to substantiate this allegation.

(7) It was alleged that the FHCRC IRB failed to ensure that prospective subjects were adequately informed of the benefits to the subject that may reasonably be expected from the research, as required by HHS regulations at 45 CFR 46.116(a)(3). Based on materials submitted by the FHCRC in its previous reports, OHRP is unable to substantiate this allegation.

(8) It was alleged that the FHCRC IRB failed to include at least one member who was not otherwise affiliated with the institution, as required by HHS regulations at 45 CFR 46.107(d). Based on materials submitted by the FHCRC in its previous reports, OHRP is unable to substantiate this allegation.

OHRP finds that the corrective actions described above adequately address OHRP's determinations. In addition, FHCRC has adequately addressed the questions raised in OHRP's letter of January 5, 2004. As a result, there should be no need for further involvement of OHRP in this matter.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects.

Sincerely,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Ms. Karen Hansen, Director, Institutional Review Office, FHCRC
Dr. Joan Clark, Chair, FHCRC IRB #1
Dr. David Maloney, Chair, FHCRC IRB #2
Dr. Paul Martin, FHCRC
Dr. William Bensinger, FHCRC
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