DEPARTMENT OF HEALTH & HUMAN SERVICES

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June 5, 2001

Jerome W. Yates, M.D., M.P.H.
Senior Vice-President of Clinical Affairs
Roswell Park Cancer Institute
Elm and Carlton Streets
Buffalo, NY 14263

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1037

Research Conducted by Dr. Steven Greenberg Using Staff Blood

Dear Dr. Yates:

The Office for Human Research Protections (OHRP) has reviewed the Roswell Park Cancer Institute's (RPCI's) March 19, 2001 report regarding the above referenced matter.

Based upon its review, OHRP makes the following determinations:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.109(a) require that the Institutional Review Board (IRB) review and approve all human subject research, unless the research is otherwise exempt under HHS regulations at 45 CFR 46.101(b). HHS regulations at 45 CFR 46.102(d) define *research* as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. HHS regulations at 45 CFR 46.102(f) define *human subject* as a living individual about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.

RCPI's report stated that (i) the peripheral blood obtained from laboratory workers, students, and fellows in Dr. Greenberg's laboratory is used to prepare DNA and RNA for "developing applied applications of molecular methodologies;" and (ii) the DNA is used "to develop....new applications of these molecular biological methodologies."

As a result, OHRP finds that:

(a) Dr. Steven Greenberg's collection of blood samples to prepare DNA to develop molecular genetic methodology constituted human subject research activities as defined by HHS regulations at 45 CFR 46.102(d) and 46.102(f).

(b) The laboratory workers, students, and fellows from whom peripheral blood was obtained to prepare DNA and RNA for research were human subjects as defined at 45 CFR 46.102(f).

(c) The human subject research activities described above were not reviewed and approved by the RPCI IRB, as required by HHS regulations at 45 CFR 46.109(a).

(2) HHS regulations at 45 CFR 46.116 stipulate that no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. OHRP finds that Dr. Greenberg failed to obtain the legally effective informed consent of the subjects participating in the above-referenced research activities.

Action 1 - Required: The RPCI IRBs must develop a plan, including both the means and the content, for contacting all subjects who participated in the above referenced research conducted by Dr. Greenberg and informing them of their previous participation in the research, the risks associated with the research, and the nature of the noncompliance by RPCI with the requirements of HHS regulations at 45 CFR Part 46. Please submit to OHRP a written report regarding the IRB's determinations and plan for this matter and the documentation underlying these determinations, including relevant IRB minutes and the proposed text for debriefing the subjects. Please forward your report so that OHRP receives it no later than July 31, 2001.

Action 2 - Required: RPCI, in conjunction with all of its investigators and clinical practioners, as well as relevant administrators, must audit and identify all on-going research projects involving human subjects that was not exempt under HHS regulations at 45 CFR 46.101(b) and confirm that all such research has been reviewed and approved by one of the RPCI IRBs. RPCI must suspend immediately any nonexempt research involving human subjects that has not been reviewed and approved by the RPCI IRB. By July 31, 2001, please provide OHRP with a report on the results of this audit and a list of any research activities that have been suspended as a result of this audit.

Action 3 - Required: Please provide OHRP with a satisfactory plan to ensure that all IRB members, all IRB staff, and all research investigators are appropriately educated, on an ongoing basis, about the regulatory requirements for the protection of human subjects, including the definitions as stipulated by HHS regulations at 45 CFR 46.102.

(3) HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution. OHRP finds that the documents in

Attachment 11, described in the report as "a copy of the completed minutes" of the IRB meetings of January 30, and February 27, 2001, failed to meet these requirements.

Action 4- Required: The RPCI must revise its policies and procedures to require that IRB meeting minutes are prepared and maintained in sufficient detail as required at 45 CFR 46.115(a)(2). By July 31, 2001, please provide copies of minutes of any IRB meetings conducted after the receipt of this letter.

(4) OHRP acknowledges that the institution has written IRB policies and procedures that adequately describe many of the activities, as required by HHS regulations at 45 CFR 46.103(b)(4) and (5). However, OHRP finds that the institution does not have written IRB policies and procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR103(b)(4) and (5).

(a) 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.

(b) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and Department or Agency head of any suspension or termination of IRB approval.

Action 5 - Required: RPCI must develop written IRB, policies and procedures that adequately describe the activities referenced at (4) (a) and (b) above.

Action 6 - Recommended: OHRP recommends that the RPCI revise its policies and procedures to require that in approving research involving prisoners or children, the IRB should make the findings as stipulated by HHS regulations at 45 CFR Part 46 Subparts C and D, respectively. OHRP strongly recommends that all required findings be fully documented in the IRB minutes, including protocol-specific information justifying each IRB finding.

(5) HHS regulations at 45 CFR 46.116 require that no informed consent, whether oral or written, may include any exculpatory language through which the subject or the subject's representative is made to waive or appear to waive any of the subject's legal rights. OHRP finds that the RPCI hospital informed consent form contained exculpatory language: "I...hereby relinquish all rights, title, and interest to such fluids, tissues, and organs."

Corrective Action: OHRP finds that corrective action has been taken to remove exculpatory language from the RPCI hospital patient consent forms and the standard protocol format for non-therapeutic studies. This corrective action appropriately addresses this finding, and is appropriate under the RPCI MPA.

(6) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk and not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. OHRP finds that the following protocols on which Dr. Greenberg was the principal investigator have not been reviewed at least once per year: protocol number CIC 91-14, "Molecular Genetic Analysis of the TCR Repertoire;" protocol number CIC 93-11, "Multiple Sclerosis and Neurobiological Tissue Repository;" and protocol number EDR 91-05, "Molecular Analysis and Antisense Modulation...."

Corrective Action: OHRP finds that corrective action has been taken to require that continuing review of all of Dr. Stephen Greenberg's research be conducted by the IRB at intervals appropriate to the degree of risk and not less than once per year.

In addition to the above, OHRP has the following concerns and questions:

(7) HHS regulations at 45 CFR 46.116(a) delineate specific elements required for informed consent.

OHRP is concerned that the IRB-approved informed consent document for the protocol entitled "Immunogenetic Study in Multiple Sclerosis and Other Neurologic Diseases," lacks (a) a clear statement that the study involves research; (b) an adequate description of any benefits to the subject or others that may reasonably be expected from the research; (c) a description of how confidentiality and privacy will be maintained; (d) an explanation of whom to contact for answers to questions about research subjects' rights (should include someone other than the investigator), and whom to contact in the event of a research-related injury to the subject. Please respond.

(8) HHS regulations at 45 CFR 46.103(f) require that an institution with an approved assurance shall certify that each *application* for research has been reviewed and approved by the IRB.

Item 4 of the General Procedures for Protocol Review and Item 2 of the Approval Procedure for New Protocols and/or Amendments Involving Change in Treatment Requiring Full Board Review in Attachment 1 of RPCI's March 19, 2001 report do not list the *application* for research as a required document for IRB review. Please respond.

(9) Item A.3. in Attachment 2 (IRB Review of Research and IRB Records) of RPCI's March 19, 2001 report states that the IRB may "waive documentation" (of informed consent) in accordance with 45 CFR 46.117. However, with the exception of 45 CFR 46.117 (c), which refers to the waiver of the requirement to obtain a signed consent form from certain subjects, the remainder of 45 CFR 46.117 is about how informed consent shall be documented. Please respond.

(10) Attachment 3 of RPCI's March 19, 2001 report is entitled Approval Procedure for New Protocols and/or Amendments Involving Change in Treatment Requiring Full Board

Review. It is unclear whether this section also applies to amendments of research that do not offer therapy. Please clarify.

(11) Item 4 b in Attachment 4 (Procedure for Conducting Continuing Review of IRB Approved Protocols) of RPCI's March 19, 2001 report states that if there is no response to the request for the required documentation for continuing review, the principal investigator is notified of pending closure to new patient accrual.

OHRP is concerned that when the approval period has expired, the notification makes no mention of research activities other than stopping the enrollment of new subjects. If the IRB does not re-approve the research, continuation of research interventions or interactions in already enrolled subjects should only continue when the IRB finds that it is in the best interests of individual subjects to do so. Please respond.

(12) In conducting the initial review of proposed research, IRBs must obtain information in sufficient detail to make the determinations required under HHS regulations at 45 CFR 46.111. Materials should include the full protocol, a proposed informed consent document, any relevant grant applications, the investigator's brochure (if one exists), and any advertising intended to be seen or heard by potential subjects. Unless a primary reviewer system is used, all members should receive a copy of the complete documentation. These materials should be received by members sufficiently in advance of the meeting date to allow review of this material.

If the IRB uses a primary reviewer system, the primary reviewer(s) should do an in-depth review of all pertinent documentation. All other IRB members should at least receive and review a protocol summary (of sufficient detail to make the determinations required under HHS regulations at 45 CFR 46.111), the proposed informed consent document, and any advertising material. In addition, the complete documentation should be available to all members for review.

It is unclear from the Agendas of the January 30, and February 27, 2001 IRB meeting and from the "Full Committee Review Procedure" described in the General Procedures for Protocol Review what informational items the IRB members receive, and whether the members receive them sufficiently in advance of the meeting date to allow review of this material. Please respond.

(13) It appears that the IRB reviews only minimal information regarding additional safeguards to protect the rights and welfare of subjects who are likely to be vulnerable. OHRP notes RPCI's statement in its March 2001 report that "children have been the only participants in clinical trials at RPCI who are considered vulnerable subjects." However, OHRP notes that the HHS regulations at 46.111(b) state that pregnant women, mentally disabled persons, and economically or educationally disadvantaged persons, are also likely to be vulnerable to coercion or undue influence. Please respond.

(14) Continuing IRB review of research must be substantive and meaningful. In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including: (a) the number of subjects accrued; (b) a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (c) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB (see OPRR Reports 95-01). Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

Based upon the informational materials provided with the agendas of the January 30, and February 27, 2001 IRB meetings, OHRP is concerned that continuing review of research by the RPCI IRB is not substantive and meaningful. Please respond.

(15) 45 CFR 46.111(a)(3) requires that in order to approve research, subject selection is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted, and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

OHRP is concerned that the IRB does not receive sufficient information to make the determinations at 45 CFR 46.111(a)(3). The RPCI Guidelines for the Preparation of Treatment Protocols appears to contain little guidance to include information regarding subject recruitment. Please respond.

Please provide your response to the above determinations, questions, and concerns so that OHRP receives it no later than July 31, 2001. Please provide a copy of the current IRB rosters with your response.

If upon further review of the concerns and questions, RPCI identifies additional 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. James P. Karr, RPCI
Dr. Barbara Bambach, RPCI
Dr. Steven Greenberg, RPCI
Dr. Greg Koski, OHRP
Dr. Melody Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Jeffrey Cohen, OHRP
Mr. George Gasparis, OHRP
Ms. Freda Yoder, OHRP
Mr. Barry Bowman, OHRP
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA