DEPARTMENT OF HEALTH & HUMAN SERVICES

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July 13, 2001

Arthur W. Nienhuis, M.D.
Director
St. Jude Children's Research Hospital
332 North Lauderdale Street
Memphis, TN 38105-2794

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1013

Dear Dr. Nienhuis:

As you know, the Office for Human Research Protections (OHRP) conducted an on-site evaluation of human subject protection procedures at St. Jude Children's Research Hospital (SJCRH) on March 12-16, 2001. The evaluation was conducted by five OHRP staff with the assistance of three outside expert consultants and one staff member from the National Cancer Institute (NCI), and also involved limited participation by representatives from the National Institutes of Health's Office for Biotechnology Activities and the Recombinant DNA Advisory Committee.

The site visit included meetings with senior institutional officials; Institutional Review Board (IRB) members; IRB administrative staff; research investigators; the Institutional Biologic Safety Officer; Institutional Biohazards Control Committee members; and staff from the Vector Production and Human Applications laboratories, the electroencephalogram laboratory, and the Department of Radiation Oncology. The evaluation involved review of the IRB files, as well as relevant research records and selected clinical records, for the following protocols: RT-1, BB98, SJMB96, SJHG98, MEMFIX-1, MEMFX-2, CANA, CYCHE, CYCHAL and CYGENE.

OHRP appreciates the great effort expended by SJCRH staff in order to provide OHRP staff and consultants with access to a large volume of documents and numerous staff members on very short notice.

A. Evaluation of Human Gene Transfer Research Protocols

Protocol title: Phase I Study of Chemokine and Cytokine Gene Modified Autologous Neuroblastoma Cells for Treatment of Relapsed/Refractory Neuroblastoma Using an Adenoviral Vector (CYCHE)
Principal Investigator: Laura Bowman, M.D.

Protocol title: Study of Cytokine Gene Modified Autologous Neuroblastoma Cells for Treatment of Neuroblastoma Using an Adenoviral Vector (CANA)
Principal investigator: Laura Bowman, M.D.

In reviewing all documents previously provided by SJCRH, as well as statements made during site visit interviews, OHRP notes the following regarding the above referenced research protocols:

(1) On or about September 8, 1999, Ms. Eva Quinley, Director of Quality Assurance for Biotechnology, and Dr. Elio Vanin, interim Director of Vector Production, discovered that (a) a vial of the Master Viral Bank (MVB) of the adenoviral vector, AvIL-2, was used to transduce autologous tumor cells injected into two subjects enrolled in the above referenced research protocols; and (b) the MVB of the AvIL-2 vector had not undergone appropriate safety testing and certification.

(2) Two lots of AvIL-2, identified as lots 6 and 7, were produced using the untested MVB of the AvIL-2 vector. As of September 8, 1999, 15 subjects enrolled in the CANA protocol and 2 subjects enrolled in the CYCHE protocol had received autologous tumor cells transduced with these lots of the AvIL-2 vector.

(3) On or about September 8, 1999, the discovery described in (1) above was communicated directly to Dr. Nienhuis and Dr. Bowman.

(4) On or about September 8, 1999, Dr. Bowman suspended enrollment of new subjects for both protocols.

(5) An annual protocol progress report for the CYCHE protocol dated October 7, 1999, and signed by Dr. Bowman that was submitted to the SJCRH IRB made no reference to the problems regarding the MVB of the AvIL-2 vector and did not disclose that subject enrollment had been suspended because of these problems.

(6) A protocol amendment for the CANA protocol dated October 12, 1999, and signed by Dr. Bowman that was submitted to the SJCRH IRB made no reference to the problems regarding the MVB of the AvIL-2 vector and did not disclose that subject enrollment had been suspended because of these problems.

(6) A protocol amendment for the CYCHE protocol dated October 27, 1999, and signed by Dr. Bowman that was submitted to the SJCRH IRB made no reference to the problems regarding the MVB of the AvIL-2 vector and did not disclose that subject enrollment had been suspended because of these problems.

(7) An annual protocol progress report for the CANA protocol dated November 17, 1999, and signed by Dr. Bowman (and revised on December 14, 1999) that was submitted to the SJCRH IRB made no reference to the problems regarding the MVB of the AvIL-2 vector and did not disclose that subject enrollment had been suspended because of these problems.

(8) In a memorandum to the SJCRH IRB Chair dated 30 November 1999, Dr. Bowman described the problems regarding the MVB of the AvIL-2 vector. There is no record that the SJCRH IRB received and reviewed this memorandum prior to January 2000.

OHRP Findings Regarding the Human Gene Transfer Research Protocols:

Based upon its review of all reports previously submitted by SJCRH, as well as additional documents reviewed and interviews conducted during its site visit, OHRP makes the following determinations:

(1) With respect to the above referenced research and the activities of the Vector Production Laboratory, OHRP found instances where the highest officials of the institution, as well as certain investigators, failed to ensure prompt reporting to the SJCRH IRB and OHRP of serious unanticipated problems involving risks to subjects or others, as required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(a) and 103(b)(5). One instance was the failure of senior institutional officials and the responsible investigators to promptly report to the IRB and OHRP the gene transfer vector problems related to the CANA and CYCHE protocols. OHRP is particularly concerned that the principal investigator for the CYCHE and CANA protocols failed to disclose the gene transfer vector problems to the IRB when submitting continuing review reports and protocol amendments one to two months after these problems were identified.

As with our findings made on November 5, 1999, during the exit interview of our previous site visit to SJCRH, these failures once again undermined the ability of the SJCRH IRB to carry out its federally mandated responsibilities related to the protection of human subjects in a manner that transcends any one study.

OHRP acknowledges that the unanticipated problems related to the CANA and CYCHE protocols have since been reported to the IRB and OHRP, and that the IRB has reviewed and appropriately acted upon this report.

(2) OHRP has reviewed your April 17, 2001 report describing SJCRH's corrective action plan to address the preceding finding which was verbally presented to SJCRH officials during our site visit exit interview on March 16, 2001. OHRP acknowledges that SJCRH has developed a detailed multifaceted education program for IRB members and staff, investigators, and institutional officials regarding protection of human subjects.

Nevertheless, OHRP finds that your corrective action plan is unsatisfactory. In specific, at the time of the OHRP's site visit exit interview on March 16, 2001, OHRP directed SJCRH to develop a satisfactory corrective action plan to ensure prompt reporting to the IRB, appropriate institutional officials and OHRP all unanticipated problems involving risks to subjects or others. The plan was to include establishment of (a) appropriate education programs for all institutional officials, investigators and research personnel to address *these reporting requirements*; and (b) open channels of communication where all SJCRH personnel are encouraged to communicate directly to the IRB any concerns regarding human subject protections. OHRP finds that SJCRH's corrective action plan fails to include either of these specific elements.

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<u>Action 1 - Required:</u> By August 10, 2001, SJCRH must submit to OHRP a satisfactory corrective action plan to ensure prompt reporting to the IRB, appropriate institutional officials and OHRP all unanticipated problems involving risks to subjects or others. In order to be considered satisfactory, the plan should include establishment of (a) appropriate education programs for all institutional officials, investigators and research personnel to address these reporting requirements; and (b) open channels of communication where all SJCRH personnel are encouraged to communicate directly to the IRB any concerns regarding human subject protections. Please note that failure to submit a satisfactory corrective action plan may result in additional regulatory actions by OHRP, including further restriction or suspension of the SJCRH MPA.

<u>B. Evaluation of Allegations Presented in OHRP's February 15, 2001 Letter</u>

Based upon its review of your February 23, 2001 report, as well as additional extensive documents reviewed and interviews conducted during its site visit, OHRP makes the following determinations:

(1) Regarding the research protocol entitled "Pilot Study of Systemic and Intrathecal Chemotherapy Followed by Delayed Radiation for Infants with Embryonal Intracranial Central Nervous System Tumors" (BB98) and the allegations related to interpretation of a head magnetic resonance imaging (MRI) study of a 12-month old subject enrolled in this research protocol, OHRP found no evidence of noncompliance with the requirements of HHS regulations at 45 CFR Part 46.

(2) Regarding the allegations related to the intrathecal administration of chemotherapy to a 3-year old patient with acute lymphoblastic leukemia, OHRP found that the patient was not enrolled in a research protocol at the time the intrathecal chemotherapy was administered. As a result, OHRP has no jurisdiction over this matter and makes no findings.

(3) Regarding the allegations related the research protocol entitled "A Phase II Study of Image-Guided Radiation Therapy for Pediatric CNS Tumors and Quantification of Radiation-Related CNS Effects" (RT-1), OHRP found no evidence of noncompliance with the requirements of HHS regulations at 45 CFR Part 46.

(4) Regarding the allegations related to interpretation of electroencephalograms (EEGs) performed under a research protocol:

(a) OHRP reviewed IRB, research, clinical, and EEG records for the following research protocols, among others:

(i) **Protocol title: Pharmacological Intervention for Learning Impaired Children Surviving Treatment for Cancer (MEMFIX1)**
Principal Investigator: Dr. Stephen Thompson

(ii) **Protocol title: Learning Impairments Among Survivors of Childhood Cancer (MEMFX2)**
Principal Investigator: Dr. Raymond Mulhern

(b) OHRP found that over the past several years there was a failure of certain investigators and senior officials at SJCRH to ensure that interpretations of EEGs performed under research protocols were documented in a timely fashion. In some cases, EEG reports were not dictated until more than five years after the EEG study was performed on a subject. In several cases evaluated by OHRP in detail for the above referenced protocols, OHRP found no evidence in subjects' clinical or research records that the EEGs were interpreted and acted upon prior to the time the EEGs were dictated.

(c) OHRP finds that the failures regarding documentation of timely interpretations of EEGs performed on research subjects (i) may have resulted in a failure to ensure that risks to subject were minimized by using procedures which are consistent with sound research design, in accordance with HHS regulations at 45 CFR 46.111(a)(1); and (ii) may have represented unanticipated problems involving risks to subject or others.

(d) OHRP acknowledges that (i) SJCRH has implemented a procedure for ensuring that reports of the interpretation of all EEGs are dictated in a timely

manner; and (ii) the SJCRH IRB has been notified of, and is evaluating, the above referenced problems related to interpretation of EEGs performed under research protocols.

Action 2 - Required: By August 10, 2001, please submit a final report regarding the SJCRH IRB's review and action regarding the above matters related to EEGs performed on research subjects, including copies of all correspondence between the investigators and the IRB and the minutes of relevant IRB meetings.

(5) Regarding the research protocol entitled "Treatment of Newly Diagnosed High-Grade Gliomas and Astrocytomas in Patients Ages ≥3-≤21 Years with a Phase II Irinotecan Window Followed by Radiation Therapy and Temozolomide" (SJHG98; Principal Investigator: Dr. Amar Gajjar), OHRP found that two subjects who did not meet eligibility criteria were enrolled without IRB approval, in contravention of the requirements of HHS regulations at 45 CFR 46.103(b)(4). In specific, the IRB-approved protocol stipulated that subjects must begin the protocol within 28 days of definitive surgery, but two subjects were enrolled more than 28 days after their definitive surgery (one subject was enrolled 42 days after definitive surgery, and a second was enrolled 32 days after definitive surgery).

OHRP acknowledges that (i) these deviations have been reported to the SJCRH IRB; and (ii) the Central Protocol and Data Monitoring Office has modified and enhanced its procedures for confirming subject eligibility. OHRP finds that these corrective actions adequately address the above finding.

C. Evaluation of the Performance of the SJCRH IRB

OHRP finds that the members of the SJCRH IRB are highly competent and well-trained. Furthermore, the Chair of the IRB is a well-respected, dedicated leader who has demonstrated an exceptional commitment to the protection of human subjects. The SJCRH IRB's initial and continuing review of research is substantive and meaningful and complies with the requirements of HHS regulations at 45 CFR 46.109-111. Furthermore, the records of the IRB are well-organized and comply with the requirements of HHS regulations at 45 CFR 46.115.

OHRP appreciates the commitment of SJCRH to the protection of human subjects. Please contact me if you have any questions.

Sincerely,

Michael A. Carome, M.D.
Director, Division of Compliance Oversight

cc: Chairman, Board of Governors, SJCRH
Dr. Victor M. Santana, IRB Chair, SJCRH
Dr. Joseph Mirro, Chief Medical Officer, SJCRH
Dr. Don Workman, IRB Administrator, SJCRH
Dr. Laura Bowman, SJCRH
Dr. Stephen Thompson, SJCRH
Dr. Amar Gajjar, SJCRH
Dr. Raymond Mulhern, SJCRH
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James McCormack, FDA
Dr. Robert Wittes, NCI
Ms. Joan Mauer, CTEP, NCI
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