DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

[March 5, 2004]

TO: Cristina V. Beato, M.D.
Acting Assistant Secretary for Health

FROM: Acting Director, Office for Human Research Protections

SUBJECT: Recommendation for Approval of HHS Support for Research Involving Children–ACTION

ISSUE

Recommendation by the Office for Human Research Protections (OHRP) that the Department of Health and Human Services (HHS) approves, with conditions, supporting the proposed research protocol entitled "HIV Replication and Thymopoiesis in Adolescents," involving the enrollment of subjects aged 13 to 24 years. In making this recommendation, OHRP has reviewed the proposed research, considered the opinions of experts, and provided an opportunity for public review and comment via a *Federal Register* Notice (no comments were received), in accordance with HHS regulations at 45 CFR 46.407.

The OHRP staff is scheduled to brief you on this issue at 11:15 a.m. on Monday, March 8, 2004.

DISCUSSION

Background: All studies conducted or supported by HHS that are not otherwise exempt and that propose to involve children as research subjects require institutional review board (IRB) review in accordance with the provisions of HHS regulations at 45 CFR part 46, subpart D. Pursuant to HHS regulations at 45 CFR 46.407, if an IRB reviewing a protocol to be conducted or supported by HHS does not believe that the proposed research involving children as subjects meets the requirements of HHS regulations at 45 CFR 46.404 (research not involving greater than minimal risk), 46.405 (research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects), or 46.406 (research involving a minor increase over minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition), and was suitable for review under the procedure provided in 45 CFR 46.407 (research not otherwise approvable which presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children), the research may proceed only if the

following conditions are met: (a) the IRB finds and documents that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and (b)

the Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determines either: (1) that the research in fact satisfies the conditions of 45 CFR

46.404, 46.405, or 46.406, or (2) that the following conditions are met: (i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (ii) the research will be conducted in accordance with sound ethical principles; and (iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in 45 CFR 46.408.

In July 2002, OHRP received a request from the University of California, Los Angeles (UCLA) Office for Protection of Research Subjects, to review a sub-study of the above-cited protocol pursuant to requirements of HHS regulations for the protection of human subjects at 45 CFR 46.407. The proposed research would be supported by National Institutes of Health grant 1 R01 AI051996-01A1 awarded by the National Institute of Allergy and Infectious Diseases (NIAID). After reviewing the proposed research, the UCLA IRB determined that it could not approve this sub-study under HHS regulations at 45 CFR 46.404, 46.405, or 46.406, but found the research presented a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children and was suitable for review under 45 CFR 46.407.

In its request for review pursuant to 45 CFR 46.407, the UCLA IRB submitted a sub-study of a proposal by Dr. Paul Krogstad that is a longitudinal study evaluating the pathogenic properties of Human Immunodeficiency Virus (HIV), the suppressive and selective power of antiretroviral therapy, and the regenerative capacity of the immune system in adolescents and young adults ages 13 to 24 years, with perinatally-acquired HIV infection, compared with two age-matched control groups: adolescents who acquired HIV infection via adult behaviors (sexual contact and illicit drug use), and seronegative adolescents. The specific aims of the study are: (1) To compare quantitative parameters of thymopoieses and T-cell turnover in adolescents and young adults with perinatal HIV infection with those from age-matched individuals with HIV acquired via recent adult behaviors and seronegative control subjects; (2) to evaluate the impact of viral factors on thymopoiesis of HIV infected adolescents; and (3) to examine the cellular immune responses of perinatally-infected adolescents. The long term aims of the study are to better understand the immunological status and prognosis of long-term survivors of perinatal HIV, and to identify possible therapeutic strategies to promote a normal, healthy lifespan for these individuals. The research protocol is proposed to take place in the General Clinical Research Center (GCRC) at UCLA. The main study would enroll a total of 60 to 90 adolescents and young adults (20-30 subjects in each group) and would involve approximately six clinic visits at six month intervals (four visits for control subjects) over a 30-month period, during which medical histories will be obtained and physical exams, blood drawing, and CT exams will be performed. At the second visit (six months following initial enrollment), approximately 5-10 subjects from each group (15 to 30 total) will be asked to participate in a sub-study of this

research protocol. During this sub-study, subjects would be admitted to the GCRC and infused intravenously over a 24-hour period with a deuterium-labeled glucose solution, and would have blood drawn at several intervals thereafter. Under the protocol, if the glucose infusion does not permit adequate labeling of immune cells, subjects would receive 70% deuterium-labeled water orally over 24 hours in the GCRC. Subjects would be sent home with additional aliquots of 70% deuterium-labeled water to be consumed 2 to 3 times per week for four weeks, and additional blood drawing would be performed during that period. (See Tab A - Research Protocol).

Review by HHS Panel of Experts: In June 2003, OHRP assembled a panel of experts in accordance with the provisions of HHS regulations at 45 CFR 46.407, and each provided his/her recommendation to the Secretary (See Tab B - Tabular Summary of Expert Recommendations). The experts possessed expertise in ethics, pediatrics, immunology, immunodeficiencies, infectious diseases (including HIV), the thymus, law and regulation. The panel also included a parent of a child with vertically-transmitted HIV/AIDS. All of the experts found that the research was approvable under 45 CFR 46.407.

Three of the panelists believed that the research was approvable under 45 CFR 46.404 ("research not involving greater than minimal risk"); additionally, one of the panelists believed that the research was possibly approvable under 45 CFR 46.404. Three of the panelists found that, as to the HIV-positive adolescents, the research was approvable under 45 CFR 46.406 ("research involving a minor increase over minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition").

All experts, as individually expressed in their reports, indicated that the research was approvable under 45 CFR 46.407, presenting a reasonable opportunity to understand a serious problem (HIV infection and AIDS) affecting the health and welfare of adolescent children. In general, the experts found that the research was not likely to directly benefit the individual subjects.

While all experts, as individually expressed, found that the protocol could be approved under 45 CFR 46.407, several experts stipulated that the protocol should be approved only after specific modifications were made to the assent/parental permission/consent documents [hereafter referred to as consent documents]. The recommended revisions to the protocol and consent documents included:

(1) fuller disclosure of confidentiality risks;

(2) information regarding treatment at no cost to participants for research-related injury as a condition of participating in the study;

(3) description of implications for females who are/may become pregnant (in terms of both confidentiality risks and risks of procedures);

(4) clarification of information provided regarding compensation for participation;

(5) clarification of the nature of information that can and will be provided back to subjects;

(6) omitting any language that may tend to conflate respective physician-investigator roles;

(7) clarifying language that conveys that participation in the sub-study at issue is distinct from participation in the main study;

(8) clarifying language on tissue storage/retention of blood samples;

(9) exclusion of glucose-intolerant individuals; and,

(10) better description of the procedures and associated risks in the study, specifically, (a) documents for the main study should be changed to indicate that a CT scan is associated with more radiation exposure than a chest X-ray and describe the specific amount of radiation to which the subject will be exposed; (b) assent form for the main study should include CT scan information in "Procedures" section; (c) timing and use of HIV confirmatory testing should be discussed in all forms, as appropriate;

Public Review and Comment: On July 16, 2003, a *Federal Register* Notice was published soliciting public review and comment, pursuant to the requirements of 45 CFR 46.407, for a period of 45 days. Documents related to the protocol were made available on the OHRP website, including the grant proposal, IRB protocol application, assent/consent/permission documents, IRB deliberations on the proposed protocol, and IRB response to questions from panel assembled under 45 CFR 46.407. No comments were received in response to the *Federal Register* Notice.

NIAID Center for Scientific Review Special Emphasis Panel (Special Emphasis Panel): During the review under 46.407 of the proposed research, OHRP considered the report of the Special Emphasis Panel, the peer-review committee convened in July 2002 to review the original grant application. The Special Emphasis Panel report found no human subjects concerns with the protocol and adequate human subjects protections in place.

OHRP RECOMMENDATION:

OHRP has reviewed the research protocol, considered the recommendations provided by the experts, reviewed the report of NIH's Center for Scientific Review Special Emphasis Panel, and noted that there were no comments received from the public. Contingent upon IRB and investigator execution of the stipulated revisions to the protocol and consent documents outlined below, OHRP finds that the research may be approved under 45 CFR 46.407, and recommends that HHS support the proposed research protocol.

OHRP bases its recommendation on the reports of experts who have reviewed this research protocol under 45 CFR 46.407, the comments of the Special Emphasis Panel (which reviewed the initial grant application), and the requirements of 45 CFR 46, subparts A and D. As noted, there were no comments received during the public review and comment period. OHRP finds that the research is not approvable under 45 CFR 46.404 because the research involves procedures that are greater than minimal risk. OHRP finds that the research may not be approved under 45 CFR 46.405 because the proposed protocol involves children (healthy and non-healthy), who are unlikely to directly benefit from participation in this research. For the healthy subjects who may be enrolled in this study who do not have a disorder or condition, OHRP finds that this research may not be approved under 45 CFR 46.406; as to the HIV-infected subjects, OHRP finds that the research may be approvable under 45 CFR 46.406 insofar as an IRB could reasonably determine that it involves research involving a minor increase over minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition, in this case HIV and AIDS.

Setting aside the other possibilities, OHRP has determined that the research protocol reaches the threshold required for approval under the provisions set forth in HHS regulations at 45 CFR 46.407, which require that the research (i) present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (ii) be conducted in accordance with sound ethical principles; and (iii) have adequate provisions for soliciting the assent of children and the permission of their parents or guardians, as set forth in 45 CFR 46.408.

OHRP finds that the research is approvable under 45 CFR 46.407 because it presents a reasonable opportunity to understand, prevent or alleviate a serious problem (i.e., HIV infection) affecting the health or welfare of children. OHRP believes that the research under grant 1 R01 AI051996-01A1 addresses a fundamentally important topic, namely the suppressive and selective power of antiretroviral therapy, and the capacity of the immune system in adolescents and young adults ages 13 to 24 years with perinatally-acquired HIV infection, compared with two age-matched control groups: adolescents who acquired HIV infection via adult behaviors (sexual contact and illicit drug use), and seronegative adolescents.

In determining whether the research would be conducted in accordance with sound ethical principles, OHRP has considered the relevant requirements set forth in 45 CFR 46, subpart A. Under HHS regulations at 45 CFR 46.111(a)(1)(i), the IRB must ensure that risks to subjects are minimized by using procedures which are consistent with sound research design and do not unnecessarily expose subjects to risk; and, HHS regulations at 45 CFR 46.111(a)(2) require the IRB to determine that risks are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of knowledge that may reasonably be expected to result therefrom.
HHS regulations at 45 CFR 46.111(a)(3) require an IRB to determine that the selection of research subjects be equitable and that the research setting be particularly cognizant of the special problems of vulnerable research populations, including children. OHRP concludes that the investigator and IRB

have taken the appropriate steps to ensure that the study population will be adequately protected.

Regarding whether adequate provisions have been made for soliciting the assent of the study subjects and parental permission, in accordance with 45 CFR 46.408, OHRP finds that the protocol satisfies this requirement.

As stated, OHRP finds that the research can be approved under 45 CFR 46.407, with stipulated revisions to the protocol and consent documents. OHRP refers to the investigators and the reviewing IRB for action the required revisions and recommendations identified below.

The required modifications are as follows:

(1) the consent forms must include a better description of the procedures and associated risks, and, specifically, a fuller description of the risks of 24-hour exposure to an IV, to include the current language, plus, a statement that more clearly describes the risk of thrombophlebitis, such as the following: "Rarely, having a needle placed in your vein can cause thrombophlebitis. This condition occurs when the vein develops severe painful inflammation and a clot forms inside the vein";

(2) timing and use of HIV confirmatory testing should be discussed, as appropriate;

(3) the consent documents must be expanded to include a fuller disclosure of confidentiality risks (including methods to protect it, and its durability);

(4) the consent documents must include a broader discussion on the issue of no-cost treatment provided to participants for research-related injury as a condition of participating in the study;

(5) description of implications for females who are/may become pregnant (in terms of possible exclusion, confidentiality risks, and/or increased risks of procedures (even if there are none));

(6) consent documents must clarify the nature of information that can and will be provided back to subjects (including use of examples and how they will be provided to subjects;

(7) consent documents must provide more clarifying language to convey that participation in the sub-study at issue is distinct from participation in the main study;

(8) consent documents must include a broader, more explicit description regarding the handling, storing, and future disposition of blood samples obtained during the course of the study;

(9) the protocol must clearly indicate that glucose-intolerant individuals will be excluded from the study, and that confirmatory sequential serum testing will be done throughout the study;

(10) the consent documents must be changed to reflect the exclusion of glucose-intolerant subjects from the study and the use of sequential serum testing; and,

(11) the IRB must seek assurance from the investigator that the compounds used in this study are prepared in accordance with the Food and Drug Administration's Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (http://www.fda.gov/cder/guidance/4286fnl.pdf), and that the protocol includes a calculation of the grams per kilogram of deuterium to be administered in each aspect of the sub-study and assurances that no subject would exceed the dose limit.

In addition, OHRP suggests that the UCLA IRB provide additional consideration to the following issues:

(1) clarification of information provided regarding compensation for participation;

(2) omitting any language that may tend to conflate the respective physician and investigator roles;

(3) expanding consent forms to include CT scan information in "Procedures" section; and,

(4) expanding consent documents to indicate that a CT scan is associated with more radiation exposure than a chest X-ray and to describe the specific amount of radiation to which the subject will be exposed.

RECOMMENDATIONS

1. Determine that HHS should support the proposed research protocol, involving the enrollment of 13- to 24-year-old subjects, with stipulated revisions to the protocol and consent documents.

2. Make this decision available to the public via appropriate methods, such as placement on the OHRP web site.

DECISION

1. Determine that HHS should support of the proposed research protocol, involving the enrollment of 13- to 24-year-old subjects, with stipulated revisions to the protocol and consent documents.

Approved /s/ Cristina V. Beato, M.D. Disapproved_____ Date [March 15, 2004]

2. Make this decision available to the public via appropriate methods, such as placement on the OHRP web site.

Approved /s/ Cristina V. Beato, M.D. Disapproved_____ Date [March 15, 2004]

/s/ Bernard A. Schwetz

Bernard A. Schwetz, D.V.M., Ph.D.

2 Attachments:
Tab A - Research Protocol: Assent for Adolescent Controls
Tab B -Tabular Summary of Experts' Recommendations