

June 23, 2003

Bernard Schwetz, D.V.M., Ph.D.
Acting Director
Office of Human Research Protections
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Dear Dr. Schwetz:

I have served on the HHS Review of Research Panel concerned with the issue of minimal risk for the research protocol entitled "HIV Replication and Thymopoiesis in Adolescents" by Principal Investigator Paul A. Krogstad, M.D.

DESCRIPTION:

The grant application seeks to fill in gaps in the information on the role of the thymus gland in HIV infection in two groups of adolescents (stated to be 13-21 years of age): perinatally infected vs. adolescently infected. Within the context of similar studies performed on adults infected with HIV and partial studies performed on children (usually less than 13 years of age), the author proposes a three-pronged attack (Specific Aims 1-3): 1) quantitate measurements of thymopoiesis, 2) evaluate the effects of viral factors on thymopoiesis, and 3) determine the extent of cellular immune responses. The author has very carefully documented the putative central role of the thymus gland in HIV infection, based upon pediatric and adult studies in HIV infection, and alluded to pediatric studies of infants with severe congenital immunodeficiencies. The author's overall hypothesis is that prolonged and poorly controlled HIV infection during childhood will cause premature immune senescence and thymic involution. The methods that the author proposes to use are those that have been applied to several adult HIV investigations. They include the use of nonradioactive labeling of T-cell populations, lymphocyte phenotyping, T-cell excision circle (TREC) assays, and computed tomography (CT) scanning (Specific Aim 1); viral DNA sequencing to look for CCR5 and *nef* mutations and examination of viral resistance to thymic organ cultures (Specific Aim 2); and ELISPOT assays for CTL responses to HIV, CMV, influenza, and EBV peptides (IFN- γ detection), lymphoproliferative responses to Candida and Tetanus recall antigens, and evaluation of the V β repertoire of CTL responses to HIV and influenza using tetramer and monoclonal antibodies to known V β clones (Specific Aim 3).

STUDY COHORTS, STUDY VISITS, STATISTICS

- PI-A: perinatally HIV-infected adolescents and young adults (most on HAART)
- AB-A: adult behavior HIV-infected adolescents and young adults (most on HAART)
- SN-A: seronegative control adolescents and young adults

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Up to 60 subjects would be enrolled in each category, but in certain studies, selected patients would be evaluated: 15 SN-A, 10 AB-A, 10 P+A (RNA <400 copies/mL), and 10 P+A (RNA >400 <10,000 copies/mL) for in vivo labeling. Study intervals would be at the start of the study and at 6-month intervals up to 30 months. Not every test would be performed at each visit (e.g., deuterium labeling experiments). Subjects would be recruited at UCLA and Children's Hospital of Los Angeles. Statistical considerations have been made for these smaller studies to ensure adequate power to detect meaningful differences (two-sided T-test [TREC], Kolmogorov-Smirnov non-parametric test ($V\beta$ repertoire) and Spearman's rank and mixed models repeated measures regression (variables relationships); and Wilcoxon's rank-sum test (group differences).

SUMMARY:

This grant proposal addresses important areas of human immune responses to HIV infection. Adolescent patients are two fold—those with HIV infection from birth and those acquired later in life (each cohort 13-21 years of age). Since the immune systems of the former group never experience a normal ontogeny, it is highly likely that the immune responses of the long-term survivors of perinatal infection will have much different immune responses to HIV than the group with a developed immune system that became infected by adult-type behaviors. This grant proposal would use state-of-the-art technology to determine how the thymus functions in these two groups. It is most likely that this research will yield new information with pertinence for further understanding of HIV pathogenesis in the two types of adolescent patients. Moreover, it is possible that new therapeutic strategies will be designed for adolescent patients, based in part upon the outcome of the research contained in this application.

HUMAN SUBJECT ISSUES:

A concern has been raised about the use of stable isotopes in control children. Stable isotopes are being used in both study and control children, even neonates, in dosages up to 3g/kg (Morey Haymond, M.D., Baylor College of Medicine Children's Nutrition Research Center, May 28, 2003). It seems, therefore, that the concern of the IRB at UCLA should be clarified, since aside from the dosage issue there appears to be no reason to not proceed with this stable isotope study in control children. This research project seems to involve no more than minimal risk to the patient, since the deuterium isotope is not radioactive. Therefore, CFR Section 46.404 (research not involving greater than minimal risk) seems applicable. Even if this protocol were considered to pose greater than minimal risk, CFR Section 46.407 would seem appropriate, since the research would represent an opportunity to further the understanding of a serious disease, the research would be conducted in accord with sound ethical principles, and adequate provision would be made for soliciting the parent's permission and the child's assent.

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There was also an issue concerning the amount of radiation from the CT examination of control children, estimated to be a cumulative 1.3 years of radiation for a child at normal atmospheric conditions (~ 20 m Gy). For comparison, a chest x-ray of a child would produce a dose of radiation approximately one-third that of a CT. In my estimation, both the CT and chest x-ray radiation exposures are quite small and amount to no more background radiation.

I do not consider, in final summary, that this research project poses any more than a minimal risk to the study subjects, including the control children (CRF 46.404).

Thank you for this opportunity to be of service.

Sincerely,

William T. Shearer, M.D. Ph.D.
Professor of Pediatrics and Immunology
Baylor College of Medicine
Chief, Allergy and Immunology service
Texas Children's Hospital

WTS:tw