May 13, 2002

Robert Figlin, M.D.
Medical Institutional Review Board
Office for the Protection of Research Subjects
2107 Ueberroth Building
169407

RE: IRB number 01-11-064-01: HIV Replication and Thymopoiesis in Adolescents – **PI response**

Dear Dr. Figlin:

Thank you for your letter of April 3rd. In response, I'd like to provide the following information.

A.

1. Thank you for your comments regarding submission to the Secretary of HHS. Please note, however, that the Committee's correspondence of December 17th, 2001 indicated that the main study risk/benefit ratio was acceptable. The Committee indicated that the **substudy** risk/benefit ratio was not acceptable, and that the **substudy** could be submitted to the Secretary of HHS for review. I appreciate the Committee's submission of this substudy to the Secretary of HHS, and I look forward to hearing from the IRB staff once the study has been reviewed. However, I believe the request that all the consent forms delete reference to "adolescents" is not appropriate, as adolescents can still be enrolled in the **main** study. In addition, our submission of assent forms for the main study was appropriate.

   Accordingly, the consent forms and assent forms for the main study have not been revised in this regard. The consent forms for the substudy have been revised to delete reference to adolescents, and we have not resubmitted the assent forms for the substudy, as no adolescents will be enrolled in the substudy pending the decision from the Secretary of HHS.

2. Thank you for your comments regarding issuing an administrative approval for this study. However, please note that deuterium labeled glucose is used only in the substudy, not in the main study as indicated in the comments. Therefore a codicil regarding information regarding the use of the deuterium label would apply only to the substudy, not the main study.
   a. The deuterium labeled compounds will be provided by Cambridge Isotope Laboratories. If glucose is used, the glucose will be administered intravenously over a 24 hour period. If deuterium labeled water is used, this will be administered orally three times a day on the first day, over at least 12 hours and possibly up to 24 hours, depending on the reaction (if any) that the subject has to drinking an increased volume of water. The amount of labeled water per dose will be based on body weight (1cc/kg). Thus a 110 lb subject would consume approximately 50 ml of water 3 times on the first day. Once at home, the subject

will be requested to consume this same amount 3 times daily for 4 days. After that, the subject will consume the same amount (50 ml in the example above) 2 times daily for one month. Again, the actual amounts per subject will vary depending on body weight. The Certificates of Analysis for the labeled glucose and labeled water are attached. Also attached is a letter from the FDA, Center for Drug Evaluation and Research, indicating, "…IND's are not required for metabolic tracer studies using isotope-enriched substances such as water, glucose…"

b. I request an administrative approval with codicil for IRB approval at Children's Hospital Los Angeles be issued.
c. Medical Radiation Safety approval is pending. I request an administrative approval with codicil pending Radiation Safety approval.
d. A copy of the revised 740 form is attached.

3. Subjects must allow a review of their medical records to participate in the research.

B.

1. A request was made to "fill-in all large gaps in each consent form". However, our copies of the consent forms show no "large gaps". We have been requested in the past to leave ample space at the bottom of each page to allow room for the IRB approval stamp. If the Committee's requirements have changed regarding the margins needed at the bottom of each page, please inform me of the new requirements. The consents attached to this form have been checked to be sure there are no "large gaps"
2. The number of subjects at UCLA and in total is already contained each consent and assent form. This was added based on the committee's request from the previous correspondence. The information can be found on page 2 of the forms.
3. The 24 hour stay is a condition of the **substudy**, not the main study. The 24 hour stay is already mentioned in the procedures section of each **substudy** consent/assent. In addition, the consents for the main study already indicate the availability of a substudy and indicate that this substudy requires a 24 hour stay. Therefore, I believe the information requested is already contained in the forms.
4. The administration of the "sugar solution" occurs only in the substudy. Therefore this request only applies to the substudy consents. These consents already indicate that the IV will be administered over a 24 hour period. Language has been added that indicates that the subjects will drink approximately ¼cup of the water solution three times over at least at least a 12 hour period.
5. The CT scan will be of the subject's upper chest – this has been clarified in the consent form.

Thank you for your rapid attention to this response. If you require further information, please contact Alison Watts in the Office of Clinical Trials at x48713.

Sincerely,

Paul Krogstad, MD
Principal Investigator