DEPARTMENT OF HEALTH & HUMAN SERVICES

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May 19, 2008

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RE: Human Research Subject Protections Under Federalwide Assurances FWA-87, FWA-315 and FWA-68

Research Project: The Use of Recombinant Growth Hormone to Enhance T-Cell Production in Adults Infected with HIV-1

Principal Investigators: Drs. Joseph M. McCune and Laura Napolitano[1]

Project Number: CHR Approval #H851-19587

Dear Drs. Mahley, Carlisle, and Washington:

[1] Please note that the December 17, 2007 letter regarding the above-referenced research inadvertently included a co-investigator in the list of principal investigators. As a result, we have changed the principal investigator list to include only those individuals who have been identified as principal investigators.

Thank you for your letter dated March 26, 2008 which was submitted in response to our letter dated December 17, 2007. In our December 17, 2007 letter we made the following determination(s) regarding the above-referenced research, among others:

(1) We determined that the University of California, San Francisco (UCSF) institutional review board (IRB) approved an informed consent document for the above-referenced research that did not include an explanation of whom to contact for answers to pertinent questions about research subjects' rights, as required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.116(a)(7), and the UCSF IRB did not approve a waiver of this requirement in accordance with the provisions of HHS regulations at 45 CFR 46.116(c) or (d).

Corrective Action: We acknowledge that UCSF has revised its informed consent form templates to ensure that the templates contain the above-referenced language. In addition, we acknowledge that UCSF has revised its IRB reviewer checklists so that that the checklists make specific reference to these requirements. We determine that these corrective actions adequately address the above determination and are appropriate under the UCSF FWA.

(2) We determined that the principal investigator for the above-referenced study initiated changes to the UCSF IRB-approved research without obtaining prior IRB review and approval as required by HHS regulations at 45 CFR 46.103(b)(4)(iii).

Corrective Action: We appreciate that UCSF continues to increase its efforts toward ensuring that the IRB is given the opportunity to review and approve all proposed changes in a research activity prior to initiation of such changes in accordance with HHS regulations at 45 CFR 46.103(b)(4)(iii), e.g., currently, IRB approval letters include language regarding investigator responsibilities under 45 CFR 46.103(b)(4)(iii), written guidance and training emphasizes the need for prior IRB approval of changes and IRB continuing review and amendment forms encourage researchers to describe amendments and report as violations any changes made without prior IRB approval. In addition, we recognize that UCSF has recently improved its required training of key personnel by adding a new training module which emphasizes the need for prior approval of changes. Lastly, we acknowledge that UCSF's Human Research Protection Program now includes a Quality Improvement Unit that performs routine on-site reviews of Committee on Human Research (CHR) approved studies, and the findings of such reviews are reported to CHR. We determine that these corrective actions adequately address the above determination and are appropriate under the UCSF FWA.

(3) We determined that the UCSF IRB failed to conduct continuing review of the above-referenced research at least once per year as required by HHS regulations at 45 CFR 46.109(e).

Corrective Action: We acknowledge that Section 2.7 of the UCSF Human Research Protection Program Procedures Manual – Convened Meetings has been revised to clarify that

continuing review for research not eligible for expedited review must occur within one year of the convened meeting of the IRB at which the research was last reviewed and given contingent approval, rather than within one year from the date that any contingencies were approved by the IRB Chair or Vice Chair. See revised Section 2.7 – Convened Meetings. We note that this change adequately addresses the determination noted above and is appropriate under the UCSF FWA. See item (5) below for additional guidance regarding continuing review.

In addition to the matter complained about, we make the following additional determinations:

(4) We find that the UCSF IRB has approved research contingent upon substantive modifications or clarifications that are directly relevant to the determinations required by the IRB under HHS regulations at 45 CFR 46.111 without requiring additional review by the convened IRB.

While we recognize that UCSF has made considerable effort to re-train IRB members and staff regarding this issue, i.e., revising the IRB Presentation Checklist and various policies in the HRPP Procedures Manual in 2005, we note that these actions may not have been adequate given that in November 2005 and October 2006 the UCSF IRB approved research contingent upon substantive modifications or clarifications that are directly relevant to the determinations required by the IRB under HHS regulations at 45 CFR 46.111 without requiring additional review by the convened IRB. In particular, OHRP notes the following:

(a) According to the November 3, 2005 IRB meeting minutes for the study *A Phase 2, Randomized, Double-Blind, Placebo-Controlled Escalating Dose-Response Trial of Intravenous Adenosine for Periopoerative Analgesia in Females Undergoing Abdominal Hysterectomy or Myomectomy*, the IRB conditionally approved this study even though the IRB asked the investigator to explain why it is in a subject's best interest to reinstate study drug after it has been discontinued as a result of cardiovascular problems. This unresolved issue is directly relevant to determining whether the risks to subjects participating in the research were minimized, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, as required by HHS regulations at 45 CFR 46.111(a)(1).

(b) According to the October 18, 2006 IRB meeting minutes for the study *A Phase III, Double Blind, Placebo-controlled, Randomized Study Comparing the Efficacy, Safety and Tolerability of Sumanirole vs. Placebo or Ropinirole in Patients with Early Parkinson's Disease*, the IRB conditionally approved this study even though the IRB asked the investigator to address the ethical considerations associated with withdrawing an FDA-approved medication from patients who are taking it prior to enrollment in the study, when they have a 66% chance of not receiving it for the duration of the study. This unresolved issue is directly relevant to determining whether the risks to subjects participating in the research were minimized, as required by HHS regulations at 45 CFR 46.111(a)(1).

Required Action: Please provide us with a corrective action plan outlining how UCSF will ensure that the UCSF IRB does not approve research contingent upon substantive modifications or clarifications that are directly relevant to the determinations required by the IRB under HHS regulations at 45 CFR 46.111 without requiring additional review by the convened IRB.

We provide the following guidance regarding UCSF's procedures regarding continuing review:

(5) Please remember that if an investigator has failed to provide continuing review information to the IRB or the IRB has not reviewed and approved a research study by the continuing review date specified by the IRB, the research must stop, unless it is in the best interests of subjects to continue participating in the research interventions or interactions. Enrollment of new subjects cannot occur after the expiration of IRB approval. See OHRP Guidance on Continuing Review, available at http://www.hhs.gov/ohrp/humansubjects/guidance/contrev0107.htm#.

We acknowledge all of the remaining UCSF responses that are not specifically addressed above.

Please provide us with responses to the above determinations by June 20, 2008, including a corrective action plan for item (4) above. Feel free to contact me if you would like guidance in developing a corrective action plan. If during your review you identify additional areas of noncompliance with HHS regulations for the protection of human subjects, please provide corrective action plans that have been or will be implemented to address the noncompliance.

We appreciate your institution's continued commitment to the protection of human research subjects.

Sincerely,

Lisa A. Rooney, J.D.
Compliance Oversight Coordinator

Cc: Mr. Donald M. Campbell, Senior Grants and Contracts Manager, The J. David Gladstone Institutes
Dr. Victor I. Reus, Chairperson, UCSF Committee on Human Research, Parnassus #1
Dr. Susan H. Sniderman, Chairperson, UCSF Committee on Human Research, San Francisco General Hospital #2
Mr. Douglas E. Eckman, Operations Manager, San Francisco General Hospital Medical Center
Ms. Sharon K. Friend, Director, Human Research Protection Program, UCSF
Dr. Alan P. Venook, Chair, UCSF IRB #4

Dr. Joseph M. McCune, San Francisco General Hospital
Dr. Laura Napolitano, San Francisco General Hospital
Dr. Sherry Mills, NIH Office of Extramural Research
Mr. Joe Ellis, NIH Office of Extramural Research