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
Telephone: 240-453-8120
FAX: 240-453-6909
E-mail: Lisa.Rooney@hhs.gov

December 17, 2007

Robert M. Mahley, M.D., Ph.D.
President
The J. David Gladstone Institutes
P.O. Box 419100
San Francisco, CA 94141-9100

Sue Carlisle, M.D., Ph.D
Associate Dean
University of California, San Francisco
San Francisco General Hospital Medical Center
UCSF/SFGH Dean's Office, NH2A21
San Francisco, CA 94110

Eugene Washington, M.D., MSc
Executive Vice Chancellor
University of California, San Francisco
Office of Executive Vice Chancellor
513 Parnassus, S115
San Francisco, CA 94143-0400

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 Investigator: Drs. Joan Lo, Joseph M. McCune and Laura Napolitano

Project Number: CHR Approval #H851-19587

Dear Drs. Mahley, Carlisle and Washington:

The Office for Human Research Protections (OHRP) has reviewed the University of California, San Francisco (UCSF) May 31, 2007 report in response to the OHRP March 26, 2007 letter

regarding the above-referenced research. OHRP acknowledges the statement that "… although the Gladstone Institutes and San Francisco General Hospital have filed their own FWAs with OHRP, both institutions are UCSF affiliates and as such are part of UCSF's Human Research Protections Program. All research conducted under the auspices of these entities is reviewed by UCSF's Institutional Review Board (IRB), the Committee on Human Research (CHR) and so the response covers all entities named in your March letter."

Based on the information submitted, OHRP makes the following determination(s) regarding the above-referenced research:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.116(a) require that when seeking informed consent, the following information, among others, should be provided to each subject:

(a) 45 CFR 46.116(a)(6): For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

(b) 45 CFR 46.116(a)(7): An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

It was alleged that a research subject was injured as a result of participating in the above-referenced research and that the researchers did not refer the subject for treatment, as was stated in the research-specific informed consent document. It was further alleged that when the human subject contacted the UCSF IRB with questions about the research, research subjects' rights, and the alleged research-related injury, the IRB did not respond to the human subject for over four months and that the subject was not referred for treatment for the research-related injury until two years after the injury occurred.

OHRP finds that the allegations could not be substantiated. Based on the information provided, it is not clear that the subject's injury, i.e., left index finger stiffness, resulted from the subject's participation in the above-referenced study. Given that OHRP could not substantiate the research-related injury allegation, OHRP does not opine on the allegation regarding the failure of UCSF to refer the subject for treatment for the research related injury until two years after the injury occurred. Notwithstanding the above, OHRP is concerned that it took the UCSF IRB four months to respond to the subject regarding the subject's alleged research-related injury. OHRP recommends that UCSF ensure that any subsequent research-related complaints be processed more expeditiously.

(2) As stated above, HHS regulations at 45 CFR 46.116(a)(7) require that when seeking informed consent, each subject should be provided with an explanation of whom to contact for answers to pertinent questions about the research and research subjects'

rights, and whom to contact in the event of a research-related injury to the subject, unless the IRB has approved a waiver of these requirements in accordance with the provisions of HHS regulations at 45 CFR 46.116(c) or (d).

OHRP finds that the UCSF IRB-approved informed consent document for the above-referenced research failed to include an explanation of whom to contact for answers to pertinent questions about research subjects' rights, as required by HHS regulations at 45 CFR 46.116(a)(7), and the UCSF IRB did not approve a waiver of this requirement.

Required Action: Please provide OHRP with a corrective action outlining how UCSF will ensure that the UCSF IRB only approves informed consent forms that contain all of the elements required under HHS regulations at 45 CFR 46.116, unless such requirements have been waived.

(3) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that an IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. OHRP finds that the principal investigator (PI) initiated the following changes to the UCSF IRB-approved research, as described in the IRB-approved protocol/informed consent form, without obtaining prior IRB review and approval:

The PI managed moderate toxicity complaints/symptoms in contradiction to what was outlined in the UCSC IRB-approved protocol and informed consent form. In specific, both the UCSF IRB-approved protocol and informed consent form provide that if subjects show any signs of moderate toxicity (including joint pain) the daily dose of GH will be reduced to 50%. If the toxicity does not resolve within 14 days, treatment will be discontinued until the problem improves. If the toxicity is still unresolved after seven days without drug, the subject will be withdrawn from the study.

In a memorandum dated September 28, 2006, the UCSF IRB raised a concern regarding whether the PI followed the UCSF IRB-approved protocol/informed consent form when the PI reduced a subject's GH therapy dose by 50% in response to the subject's carpal tunnel syndrome symptoms that presented on November 24, 2003, but did not hold GH therapy (when the symptoms did not resolve within the 14 days that the subject received 50% reduced GH therapy) and did not permanently discontinue the subject from the study when the subject's symptoms remained unresolved after 7 days without drug. In a memorandum dated October 12, 2006, the PI admitted to this protocol deviation, provided a justification for the protocol deviation, submitted a revised protocol/informed consent form to: (1) more clearly describe management of toxicities and; (2) list tendonitis as a possible study side effect. OHRP commends the UCSF IRB for identifying this protocol deviation notwithstanding the following September 12, 2006 QUI directed site visit statement "File review indicated that study implementation and protocol management for participant 750-007 was conducted per protocol."

Required Action: Please provide OHRP with a corrective action ensuring that the UCSF IRB will review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects.

(4) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk, but not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. Additionally, where the convened IRB specifies conditions for approval of a protocol that are to be verified as being satisfied by the IRB Chair or another IRB member designated by the Chair, continuing review must occur no later than one year after the date the protocol was reviewed by the convened IRB, not on the anniversary of the date the IRB Chair or his or her designee verifies that IRB-specified conditions for approval have been satisfied.

OHRP finds that the UCSF IRB failed to conduct continuing review of the above-referenced research at least once per year. Specifically, the convened IRB conditionally approved the above referenced research on October 18, 2001, but the study did not undergo subsequent IRB review and approval until November 7, 2002, more than one year after the date the protocol was reviewed and conditionally approved by the convened IRB.

Required Action: Please provide OHRP with a corrective action outlining how UCSF will ensure that the UCSF IRB conducts continuing review of research at intervals appropriate to the degree of risk, but not less than once per year as required by HHS regulations at 45 CFR 46.109(e). In formulating your corrective action, UCSF may want to consider revising section 2.7.11.3 [Response Required – To be reviewed by Chair (also called "Contingent Approval")] of the UCSF Human Research Protection Program Procedures Manual 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 reviewed and given contingent approval, rather than within one year from the date that the contingencies were approved by the IRB Chair or Vice-Chair.

OHRP has the following questions and concerns regarding the UCSF system for protecting human subjects:

(5) [Redacted]

[Redacted]

[Redacted]

[Redacted]

OHRP has the following questions and concerns regarding CHR Approval #H851-19587:

(6) [Redacted]

(7) [Redacted]

OHRP has the following questions and concerns regarding the UCSF system for protecting human subjects:

(8) [Redacted]

OHRP has the following recommendations regarding the UCSF Human Research Protection Program Procedures Manual (dated October 2005):

(9) [Redacted]

(10) [Redacted]

(11) [Redacted]

[Redacted]

(12) [Redacted]

(13) [Redacted]

(14) [Redacted]

[Redacted]

Please submit your response to the findings, questions and concerns noted above so that OHRP receives them no later than February 8, 2008. 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.

OHRP appreciates your institution's continued commitment to the protection of human research subjects. Do not hesitate to contact OHRP if you should have any questions regarding this matter.

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. Joan Lo, San Francisco General Hospital
Ms. Sherry Mills, NIH Office of Extramural Research
Mr. Joe Ellis, NIH Office of Extramural Research
Dr. Ivor Pritchard, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Ms. Shirley Hicks, OHRP
Dr. Irene Stith-Coleman, OHRP
Dr. Kristina Borror, OHRP
Ms. Patricia El-Hinnawy, OHRP
Ms. Kelley Booher, OHRP
Mr. Barry Bowman, OHRP