Staff Evaulation

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Complaint About Human Research Collaboration on Malariotherapy

PI's March 21, 2003 response to IRB February 14, 2003 correspondence.

The Medical Institutional Review Board (MIRB) received additional information regarding your alleged participation in malariotherapy research and your letters of January 9 & 10, 200?

The MIRB reviewed the material during the meeting of January 29, 2003. The MIRB noted that the new information may indicate you were "engaged" in human subjects research as defined by the Federal regulations, 45 CFR 46, and the Department of Health and Human Services-Office of Human Research Protections (DHHS-OHRP) guidelines. Please note: the MIRB did not consider your assessments of the malariotherapy research as subject to its inquiry.

The Board requests your response to the following issues related to the conduct of human subjects research by March 14, 2003.

PI Response:

This responds to the Letter of February 14, 2003 from the OPRS.

I understand that an issue for the OPRS is whether the UCLA contacts[1] with Dr. Xiao Ping Chen and his malariotherapy research were such that UCLA was engaged in human subjects research as an investigator with Dr. X.P. Chen. Thank you for directing me to the definitions of research found in 45 C.F.R. 46. I believe that application of those definitions establish that UCLA's contacts with Dr. X.P. Chen's research did not make UCLA an investigator in that research. In other words, there was no UCLA research with Dr. Xiao Ping Chen.

As is pointed out in the UCLA OPRS Investigator's Manual for the Protection of Human Subjects, research is defined in 45 C.F.R. 46 as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge." Human subjects research is defined as research with subjects who are "living individual(s) about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information." The UCLA contacts with Dr. X.P. Chen will be explained below and did not amount to a systematic investigation. In particular, there was no intervention and no interaction with human subjects conducted by UCLA. In other words, UCLA had no human subjects involvement since any data received or analyzed at UCLA were <u>not</u> obtained by intervention or interaction with any human

[1] By UCLA contacts, I mean any contacts by me or any UCLA personnel of which I am aware.

subject by UCLA. Also, the information which was provided to UCLA was not identifiable private information.

Identifiable private information is defined by 45 C.R.F. § 46.102(f)(2) as information which is "individually identifiable (i.e. the identity of the subject is or may readily be ascertained by the investigator or associated with the information)". I most emphatically state that neither I nor, to my knowledge, any other UCLA contact was provided with any such individually identifiable information concerning Dr. X.P. Chen's malariotherapy research. The samples brought and the data provided to UCLA concerning Dr. X.P. Chen's research did not allow us to ascertain or to identify the particular individuals who were the source of the samples or data. We did not request or receive any individually identifiable information for any of the samples or data from

Dr. X.P. Chen's research. (The only samples from that research brought to UCLA were samples brought by Dr. X.P. Chen to UCLA when he was here in 1997 for Fogarty grant purposes. Those samples came from a 1994 study previously completed without UCLA involvement.) Using the terms you suggest, all samples and all data provided from Dr. X.P. Chen's malariotherapy research to his UCLA contacts were unlinked. We could not and did not obtain unidentifiable private information for any research subject.

The answers to the specific questions in the OPRS February 14, 2003 letter are as follows.

{Staff Note:
The DHHS-OHRP Engagement Guidance indicates an institution is engaged in human subjects research when:

A(5) Institutions whose employees or agents obtain, receive, or possess private information that is individually identifiable (either directly or indirectly through coding systems) for research purposes (e.g., obtaining private information from medical records in an individually identifiable form). (However, see Examples (B)(7) and B(8) for certain activities involving the release of information and/or specimens to investigators in non-identifiable form.)

Institutions are NOT engaged in human subjects research when:
B(7) Institutions whose employees or agents release information and/or specimens to investigators in non-identifiable (i.e., non-linkable) form, where such information/specimens have been obtained by the institution for purposes other than the investigators' research (e.g., nursing home employees provide investigators with a data set containing medical record information, but the data set contains no direct or indirect identifiers through which the identity of individual subjects could be ascertained, either by the investigators or by nursing home personnel; a hospital pathology department releases excess tissue specimens and relevant medical record information to investigators, but these materials include no direct or indirect identifiers through which the identity of individual subjects could be ascertained, either by investigators or by hospital personnel, including the pathology department; consistent with applicable law or recognized authority, local hospitals or health departments permit State or Local Health Department investigators to access information for research purposes, but the investigators

record no direct or indirect identifiers through which the identity of individual subjects could be ascertained, either by the investigators or by local hospital or health department personnel.)

B(8) Institutions whose employees or agents receive information or specimens for research from established repositories operating in accordance with

- *(i) an applicable OPRR-approved Assurance;*
- *(ii) OPRR guidance (see http://ohrp.osophs.dhhs.gov/humansubjects/guidance/reposit.htm); and*
- *(iii) written agreements unequivocally prohibiting of release of identifying information to recipient investigators.}*

1. The MIRB previously noted that you do not appear to be engaged in human subjects research related to the allegations from "Dr. Bob Smith". The IRB's determination was based in part on your October 17, 2002 statement, "I have not been 'working in conjunction' with the Heimlich Institute" and similar statements in response to our October 2002 inquiry. As a result of the Board's determination, Campus Counsel Patricia Jasper sent a letter to Dr. Henry Heimlich. The MIRB, therefore, was surprised to receive Dr. Heimlich's documentation indicating your possible involvement in malariotherapy research.

    a. For example, your August 8, 1996 letter to Dr. Heimlich offers assistance in measuring cytokine levels "in selected patients treated with malariotherapy." Your January 9, 2003 letter to Ms. Jasper indicates the August 8, 1996 correspondence "...is an initial exploratory letter without commitments. It enabled us to get the address, etc., of the lead Chinese investigator, Dr. Xiao Ping Chen." Yet, the August 8, 1996 letter outlines a dual intent. The first intent or in your words, "context", offers your laboratory's assistance, as noted above. The second "context" offers to "...develop a means of helping [Dr. Heimlich's] Chinese colleagues in carrying out their studies. Assistance with reagents and quality control samples for CD4 measurements as well as for other parameters of HIV infection." Please clarify whether Dr. Chen was encouraged to bring biological samples from the malariotherapy research to UCLA as a result of your August 8, 1996 letter and your subsequent recruitment of him for participation in the Fogarty training grant.

PI Response
Regarding my August 8, 1996 letter to Dr. H. Heimlich and the contexts:
Do you mean to ask me to explain the two contexts? "Assistance" was meant to be training. That was in the context that Dr. Heimlich was making unwarranted claims for Dr. X.P. Chen's research. Dr. Heimlich claimed CD4 T cell increases based on an unproven methodology (not the methodology—flow cytometry— which we and others in the U.S. were using). Training people to be knowledgeable about AIDS research—i.e., about good and not good methodologies, about quality control, etc.—was part of the Fogarty program.

No. Dr. Xiao Ping Chen was not encouraged to bring biological samples from malariotherapy research to UCLA as a result of the August 8, 1996 letter and subsequent recruitment of Dr. X.P. Chen for participation in the Fogarty training grant.

b. Your August 6, 1997 letter to Dr. Heimlich included "tables of the data obtained on the samples provided by Chen Xiao Ping." The letter indicates tests performed at UCLA on samples 4001, 4002, 4003, 4004, 4005, 4006, 4007, and 4008. The letter informs Dr. Heimlich to "please feel free to use this data in reports and publications. We would appreciate an acknowledgement and credit to the support provided by NIH grants TW 00003 and AI 36086." Your October 17, 2002 letter to the MIRB, however, indicates samples "...independently brought by Dr. X.P. Chen to UCLA and tested by Dr. X.P. Chen were identified only by serial numbers (1,2,3, etc.) and could not be linked to the subjects." Furthermore, your November 6, 1998 letter to Dr. Chen acknowledges the difficulty of performing clinical research and appears to indicate the samples are not anonymous or anonymized but rather coded with direct or indirect codes that could be linked to direct subject identifiers ["... to maintain continued follow-up contact, obtaining blood samples, seeing that appropriate analyses are done and that the data is collected is an enormous task."]. Please clarify whether the above referenced biological samples analyzed in UCLA facilities were coded, unlinked, or unidentified. If the samples were coded, please provide a detailed description of the code, e.g., the information from donors linked to the code, and identify the individuals who held or hold the links to the code.

Please use the following National Bioethics Advisory Commission (NBAC) definitions[2] to guide your response to the request:

Coded Samples: Sometimes termed "linked" or "identifiable," these samples are supplied by repositories to investigators from identified specimens with a code rather than with personally identifying information, such as a name or a Social Security number. The code could be used to link personal identifying information with the sample.

Unlinked samples: Sometimes termed "anonymized," these samples lack identifiers or codes that can link a particular sample to an identified specimen or a particular human being.

Unidentified Samples: Sometimes termed "anonymous," those specimens for which identifiable personal information was not collected or, if collected, was not maintained and cannot be retrieved by the repository.

PI Response
The letter of August 6, 1997 is forwarding tables that, I believe, were prepared by Dr. X.P. Chen.

[2] National Bioethics Advisory Commission, Research Involving Human Biological Materials: Ethical Issues and Policy Guidance, Rockville: August 1999.

I do not know where the 4000 series of numbers came from. My only information is that Dr. X.P. Chen brought samples labeled 1 to 51. I do not have any records with tests of samples in a 4000 series. Dr. X.P. Chen took the data with him. I surmise that Dr. X.P. Chen prepared the tables.

The samples that were brought by Dr. X.P. Chen to UCLA were tested without any knowledge of the patients' identification by UCLA personnel. We had no knowledge of a code—just the numbers 1 to 51 as stated previously. The samples could not be linked by us to any study subjects. For us, the samples were unlinked. In retrospect, it appears that Dr. X.P. Chen may have had links between the 1, 2 and 3 code and the patients in his study.

The training faculty at UCLA (J.L. Fahey and Najib Aziz) were not investigators in the Guangzhou studies. Dr. Xiao Ping Chen and his colleagues were the investigators. The studies were done in Guangzhou, China. We did not secure the samples. We did not code the samples. We did not have the clinical information. We did not have the patients' names. We did not have (and do not have) any codes that linked laboratory data to subject identifiers.

Dr. Xiao Ping Chen, the investigator, may have had some means of linking data, but he did not share that with us.

2. Your September 18, 1998 email to Dr. Chen notes, "However, it would be interesting to review your preliminary data with both HIV- and HIV+ populations in Guanzhou. We do not expect that the data would be the same in both locations, but a look at the initial data might be advantageous at this time, particularly if more reagents will be needed. Separately, of course, there is the interest in the clinical and laboratory status of the participants in your study of malarial therapy. It would be interesting to know how many febrile episodes each of the recipients had and any other clinical manifestations of the malarial infection or of HIV induced AIDS. Also, the CD4 T-cell levels and other laboratory parameters that you have been able to measure should be quite interesting. I do hope that you will be willing to share that with me." The email also seems to suggest there were identifiers linked to the coded samples that would enable connecting outcome to possibly identifiable clinical information.

   a. Please clarify whether you or other UCLA personnel were provided with any such data described in your September 18, 1998 email during or after the visit to China. If so, please explain the nature of the data and describe the method of coding using the NBAC definitions outlined above.

PI Response
The work was done in Guangzhou. The question about comparing data on HIV-positive and HIV-negative populations was a quality control issue. Could the 1998 Guangzhou CD4 T cell testing procedures discern the expected differences? I do not remember seeing the primary data, but rather a statistical rendering of the data from both groups—mean, SD, etc. I do not recall seeing any information that was

individually identifiable. I do not believe any other UCLA personnel saw the primary data or any individually identifiable information. It seems likely that Dr. X.P. Chen had identifiers. The method of coding was not shared with me or any other UCLA personnel. Neither I nor any other UCLA personnel had any identifiers.

b. The same email indicates, "We can discuss the shipment of samples for viral load determination. It would be reasonable to wait until I have visited Guangzhou before sending any samples here." Please clarify whether such samples were sent to UCLA or any other facility in the USA.

PI Response
No such samples were sent to UCLA . I do not know if Guangzhou samples were sent to any other facility in the U.S.

3. A September 25, 1998 email from "Eric" through Dr. Chen's email account to Dr. Heimlich indicates in part, "This foundation has told [sic] that we will not be able to get any funding for additional patients until Dr. Heimlich and Dr. Fahey present the results on the current patients, especially the viral loads." Your January 9, 2003 letter to Ms. Jasper indicates the email is "Misleading." Please explain why the email is "misleading."

PI Response
The statement is misleading, because it implies that I had, or was going to have, viral load data. I never had viral load data. It also implies that I was preparing for a presentation with Dr. Heimlich.

I never would have participated in it, if I had been requested to do so.

a. Please identify "Eric" and describe his relationship to the Fogarty grant, the malariotherapy research, or UCLA.

PI Response
Eric Spletzer was an associate of Dr. H. Heimlich in Cincinnati who seemed to be an employee of the Heimlich Institute. He had no relationship to the Fogarty grant or to UCLA. E. Spletzer's relationship to malariotherpy research seemed to be as an agent or representative of Dr. Heimlich in relation to Dr. X.P. Chen.

b. Additionally, please describe the nature of the presentation referred to in the email and whether you participated in such a presentation.

PI Response
I cannot describe the nature of the presentation referred to in the e-mail. I never heard of it (or any other presentation with Dr. Heimlich) until December 2002.

4. Your November 10, 1998 email to Dr. Chen requests the exclusion of Dr. Najib Aziz and you as co-authors on "the 2nd study." Rather, you suggest "it is more appropriate if you simply acknowledge assistance.... we should not be among manuscript authors at this time." Please explain why you and Dr. Aziz declined co-authorship "at this time."

PI Response
"At this time" was a courtesy phrase. The sentence was written to remind Dr. X.P. Chen that Dr. Aziz and I were not part of the malariotherapy research study. Dr. X.P. Chen had repeatedly asked us to be authors. We always refused because it was not our research. Such requests are not unusual in developing countries where the investigators believe there is some added recognition if a co-author is from a leading U.S. or European medical center.

a. The email also indicates "...it will certainly facilitate making judgments about tests where the results appeared to changed [sic] substantially during the malarial period as well as subsequently. We hope to be of assistance in this data analyses. The data for the CD4 and CD8 measurements obtained at the 1 month and 3 month time points after the end of malarial infection will also be interesting to see." Please clarify if you or Dr. Aziz were provided with such information.

PI Response
The suggestion for providing assistance in data analysis was a mentoring function. Dr. X.P. Chen (and Dr. Heimlich) did not appreciate the variability inherent in CD4 T cell and other measurements. If only one of several post-treatment data points for a patient was higher than the baseline, Drs. X.P. Chen and Heimlich had been interpreting the data as showing that an increase in CD4 T cells had occurred. The notion of a confirmed increase, e.g. two sequential tests showing an increase of more than a pre-determined amount (perhaps, 100/mm CD4 T cells) over the mean baseline level seemed to be difficult for them to understand or accept. An example of my effort to educate about the proper techniques of scientific data analysis is my letter to Dr. X.P. Chen of August 17, 1999 and, again, in 2002.

Dr. X.P. Chen wanted very much to show that CD4 T cell levels were increased. A part of my mentoring function was to help Dr. X.P. Chen focus and understand what was happening in his study. In that context, I did see data on the study patients, but without any identifiable private information. In this type of study, good and bad events can be obscured by using averages. Valid research methodology requires the data on individual subjects to be evaluated.

b. If so, please outline the coding system applied to the data, using the NBAC definitions described above.

PI Response
The data were coded, but I never had access to the code. As far as I was concerned, the data were unlinked.

5. Please provide the full title and IRB number, if applicable, for the grant referenced as AI 36086.

PI Response
AI 36086—Epidemiology of Cytokine Dysregulation in HIV Disease. 07/01/94 – 01/31/98 plus two-year no cost extension to 01/31/00. HSPC-08-346 was obtained for blood from normal subjects to establish control standards in laboratory tests for AIDS and immune function investigations.

6. The MIRB acknowledges your December 30, 2002 response wherein you provided assurance that UCLA IRB approval or Certification of Exemption would be required "...for any and all individuals who wish to work with human biological materials or data for research purposes and work in my laboratory or participate in scholarly programs under my supervision, such as the grant from the Fogarty International Center."

PI Response
Thank you for the acknowledgement.

7. Please provide the Board with any other information you think is pertinent to the review of the allegations.

PI Response
Any other information: There are various references to, possibly, shipping samples from China to UCLA for viral load testing. However, no samples were ever shipped. The UCLA laboratory never did any viral load assays—not for anybody. I believe Dr. X.P. Chen set up a viral load test procedure in his labs in Guangzhou. We encouraged him to do that.