DEPARTMENT OF HEALTH & HUMAN SERVICES

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November 22, 2004

Richard C. Powell, Ph.D.
Vice President for Research and Graduate Studies
University of Arizona
Administration Building, Room 601
P.O. Box 210066
Tucson, Arizona 85721-0066

RE: Human Research Subject Protections Under Federalwide Assurance (FWA) 4218

Research Project:	A Prospective Randomized, Open-Label, Comparative, Clinical Trial in Post-Surgical Melanoma Patients with Either DNP-Modified Autologous Tumor Vaccine or Interferon Alpha 2-b
Principal Investigator:	Evan Hersh, M.D.
Protocol Number:	HSC # 01-64

Research Project:	Vehicle-Controlled, Double-Blind Study to Assess the Safety and Efficacy of Immiquimod 5% Cream for the Treatment of Superficial Basal Cell Carcinoma
Principal Investigator:	Norman Levine, M.D.
Protocol Number:	HSC # 01-18

Dear Dr. Powell:

The Office for Human Research Protections (OHRP) has reviewed the University of Arizona's (UA's) November 18, 2003 report that was submitted in response to OHRP's July 8, 2003 letter to UA regarding allegations of possible noncompliance with the Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR part 46) involving the above-referenced research. OHRP has also reviewed UA's November 4, 2003

report that was prepared by a "Blue Ribbon" Panel (Panel) specifically convened by UA to conduct an investigation into the allegations presented in OHRP's July 8, 2003 letter. OHRP acknowledges that no subjects were enrolled in protocol HSC # 01-64.

Based upon review of the November 4 and November 18, 2003 reports, OHRP makes the following determinations regarding the allegations presented in OHRP's July 8, 2003 letter:

(1) HHS regulations at 45 CFR 46.111(a)(1) require the Institutional Review Board (IRB) to determine that risks to subjects in research are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk. It was alleged that protocol HSC # 01-18 required all subjects to undergo a post-treatment wide-angle excision which may lead to unnecessary facial scarring, and that dosing of the test agent was not done based on the size of the lesion. In addition, it was alleged that protocol HSC # 01-64 placed subjects at an increased risk of death due to a failure of the study to offer all enrolled subjects interferon therapy and to monitor patient survival adequately.

With regard to protocol HSC # 01-18,

(a) UA's November 4, 2003 Panel summary report stated the following in response:

> "By reading the protocols and the IRB minutes in which HSC # 01-18 was discussed, the Panel found that there was no wide-angle excision planned in the protocols and that there was explicit details [*sic*] on the increased dose to be given with the increased size of the lesion."

(b) Protocol HSC # 01-18 issued dated November 17, 2000 stated the following:

(i) "**Posttreatment Target Tumor Excision**

> Twelve weeks following completion of treatment with the study cream, subjects will have the entire target tumor site surgically excised, including a 3-4 mm margin around the original tumor margins, if the target tumor is clinically evident. If the tumor is <u>not</u> clinically evident, excision margins of 1-2 mm around the original tumor margins are acceptable...."

(ii) "**Subject Instructions**

Subjects will also be instructed as to how much cream should be applied with each dose, based on the size (larger diameter) of the target tumor...."

(c) Dr. Levine's February 2, 2002 letter to Dr. David Johnson, Chair, UA IRB, in response to UA IRB's January 23, 2001 letter to Dr. Levine regarding protocol HSC # 01-18 stated the following:

(i) "Nowhere in the protocol, consent form or PAF [Project Approval Form] is there any mention of performing wide-angle excisions. A simple excision will be done to include a **3-4 mm (not cm)** [emphasis in original] margin if the tumor is clinically evident and a **1-2 mm (not cm)** [emphasis in original] margin if the tumor is not clinically evident. (page 21 of protocol) This procedure is an acceptable treatment method for the removal of BCC's [basal cell carcinomas] and is frequently used by practicing dermatologists throughout the world. A scar will ensue but it is inevitable by whatever means is used for evaluation of the tumor.... Subjects in the study with facial BCC's will be selected based on where the BCC is located. Exclusions include within 1 cm of the ears, eyes, nose, mouth, and hairline.... The informed consent states that an area larger than the tumor site will be removed, the area will be sutured and the wound may heal with a scar. We will change the 'may' to 'will' heal with a scar, as the procedure will create some form of scar. This scar will be no different that [*sic*] one created by a plastic surgeon excising the tumor by the most common method of removal, namely elliptical excision. Therefore, we don't see the need to delete facial lesions from the study."

(ii) "Reference to dosing is located on page 28 in the protocol in the chart. The dosage depends on the size of the tumor."

With regard to protocol HSC # 01-64,

(d) UA's November 4, 2003 Panel summary report stated the following in response:

"It is also clear from reading the protocols, the literature and the IRB minutes for project HSC # 01-64, that the equivalency trial, in which ATV [autologous tumor vaccine] was to be compared to IFN [interferon alpha

2-b] in advanced melanoma, 'was appropriate and did not expose the subjects in the ATV group to increased risk of death from melanoma.' Furthermore, 'the equivalency trial had appropriate monitoring strategies in place to prevent an ongoing imbalance in patient outcome and to monitor patient status including relapse rate and serious medical events including mortality.'"

(e) The investigator's brochure stated the following:

"In post-surgical adjuvant patients, use of the DNP-vaccine as a surgical adjuvant with what is now recognized as an optimal or near-optimal regimen, has shown encouraging efficacy, with 1, 2, 3, 4, and 5-year relapse-free survival times exceeding those after use of non-DNP-vaccine, as well as those published for either interferon-alpha or no post-surgical therapy. Five-year overall survival was also clearly better with the DNP-vaccine in study 4.2, compared to published results with interferon-alpha, a result suggested by a second study (9.2). Other studies did not show this apparent benefit of the DNP-vaccine over interferon, a finding hypothesized to be the result of less-than-optimal dosing regimen."

(f) UA's November 4, 2003 Panel subcommittee report stated the following:

"Review of the literature regarding interferon therapy for melanoma that was available at the time of the study and that has appeared since indicates that this adjuvant treatment is of questionable benefit as compared to placebo. A systematic review regarding the use of IFN in melanoma treatment that was published in April of 2002 concluded that the results from the acceptable, randomized, controlled, trials 'demonstrated no clear benefits of IFN [alpha] therapy on overall survival in melanoma patients'.... This review included rigorous scientific publications from 1966 through March, 2001; i.e. the date of the IRB review of Study #01-64. Further, it is clear that the administration of IFN is commonly associated with greater toxicity than would have been anticipated with the study medication (ATV)."

"Review of the protocol for this study ... demonstrates that it included a detailed description of study monitoring procedures including clear a priori definitions of adverse medical events, reporting procedures, and the contact information for real-time (within 24 hours) reporting of all serious medical events to the study monitor...."

> "The statistical analysis plan ... indicates a plan for sequential analyses of this study. There were to be two interim analyses. The first would have occurred after the 78th of 235 anticipated relapses and the second after the 157th relapse. Group sequential methods described by O'Brien and Fleming were to be used at the 0.0005 and 0.014 levels to assess treatment imbalance. The statistical description of these interim analyses and their impact on the subsequent final analysis of the study was appropriate...."
>
> "Although the interim analyses were based upon relapse and not mortality, it is unlikely that there would have been a treatment imbalance in mortality due to factors other than melanoma recurrence and thus, this strategy would have protected against an imbalance in survival; i.e. a difference in relapse should have been seen well before a difference in survival could be detected. Thus, there was an appropriate monitoring plan in place for serious adverse medical events and planned sequential monitoring for treatment imbalance at approximately 1/3rd to 2/3rd through the study."

(g) Dr. Hersh's April 17, 2001 letter to Dr. Johnson, Chair, UA IRB, in response to UA IRB's March 13, 2001 letter to Dr. Hersh regarding protocol HSC # 01-64 stated the following:

> "The justification for this randomized trial which offers an experimental vaccine to half the patients and 'standard treatment' is that the hypothesis being tested is that the vaccine will be at least as effective or more effective than interferon. This is based on the preliminary studies with this vaccine. This protocol utilizes a standard phase III approach. In addition the vaccine in over 300 patients has been demonstrated to be much less toxic or almost non-toxic compared to the highly toxic interferon. Furthermore, it is essential that we develop better and less toxic adjuvant therapy for stage III melanoma in that many of these patients still relapse. Furthermore, many do not tolerate interferon after it is started. Finally, we don't offer interferon to people over the age of 70 because we know in advance that they cannot tolerate it."

(h) Dr. Hersh's June 20, 2001 letter to Dr. Tom Hixon, Vice President for Research, UA, regarding protocol HSC # 01-64 stated the following:

> "Finally, [name deleted] ... suggests a design of high dose Interferon versus high dose Interferon plus vaccine. I would not favor this design on

> a scientific basis. Thus, high dose Interferon is believed to act as a direct cytotoxic and cytostatic agent to melanoma cells and also as an antiangiogenesis agent. It is known to substantially suppress both the white blood cell count and the lymphocyte count in most patients. I observed 20 years ago that it actually inhibited mitogen-induced lymphocyte proliferation in vitro. It also produces a high level of physiological stress including fever, chills, nausea, vomiting, diarrhea, flu-like symptoms, etc. Thus I think it is very likely to be immunosuppressive and I would not combine it with a vaccine."

Based on the statements above and OHRP's review of other information presented in your report, OHRP finds that the above allegations were not substantiated.

(2) HHS regulations at 45 CFR 46.111(a)(2) require that the IRB determine that risks to subjects in research are reasonable in relation to anticipated benefits, if any, to subjects. It was alleged that the risks to the subjects involved in protocol HSC # 01-64 were not discussed when the study was reviewed by the IRB on March 13, 2001.

(a) UA IRB's March 13, 2001 letter to Dr. Hersh regarding the UA IRB's review of protocol HSC # 01-64 stated the following:

> (i) "Interferon side effects are not stated clearly - 'read package insert' is not adequate and statistics provided are inconsistent with consent form."
>
> (ii) "Justify withholding standard therapy from 100 patients with unproven vaccine."

(b) UA's November 4, 2003 Panel summary report stated the following in response:

> "'The minutes for the IRB meeting held on 13 March 2001, and a letter sent to Dr. Hersh on the same date clearly indicate attention to the withholding of standard therapy in the group receiving the vaccine.' The IRB specifically required the PI to elaborate more on the side effects of IFN therapy and to justify withholding of standard therapy (IFN) from patients receiving an unproven vaccine. Dr. Hersh responded by clarifying IFN toxicities in a revised Project Approval Form, and further clarified the need for a better, less toxic adjuvant therapy. The IRB subsequently approved this study and communicated this to Dr. Hersh on 8 May 2001. The Panel found that the risks to subjects in relation to

potential benefits

were appropriate and that the IRB reviewing HSC # 01-64 fulfilled its role by addressing the risks and benefits of this trial."

(c) UA's November 4, 2003 Panel subcommittee report stated the following:

(i) "This Phase II equivalency trial comparing IFN and ATV adjuvant therapy in patients with advanced melanoma had an appropriate risk-benefit balance for subjects by virtue of true equipoise as regards the two treatment strategies and appropriate study conduct plans and monitoring procedures."

(ii) "The IRB addressed the two main risks in this protocol, namely the toxicity of IFN and the risk of using ATV without IFN in the ATV group. The IRB ensured that the risk/benefit balance was appropriate."

Based on the statement in (1)(g)above, the statements in (2)(a)-(c) above, and OHRP's review of other information presented in your report, OHRP finds that the above allegation was not substantiated.

(3) HHS regulations at 45 CFR 46.116(a)(2) require that the informed consent document include a description of any reasonably foreseeable risks or discomforts to the subject. It was alleged that the informed consent document for protocol HSC # 01-18 failed to include the risks of scarring and flu-like symptoms. In addition, it was alleged that the informed consent document for protocol HSC # 01-64 failed to include an adequate description of the risks of the study.

(a) UA's November 4, 2003 Panel summary report stated the following in response:

"While the originally submitted informed consent forms were seen as lacking, the concerns of the IRB members were expressed to the investigators and in both projects, more specific consent forms were developed. The Panel found that the final approved consent form for HSC # 01-64 'contained appropriate descriptions of risks, benefits, and potential discomforts. The informed consent was clear about the standard therapy (IFN) and its' [*sic*] likely benefit in contrast with the experimental therapy (ATV) and its potential lack of benefit.' Similarly, the Panel found for project # 01-18 that the IRB process was effective. 'Concerns

about untoward risks to patients were voiced and debated. The IRB's concerns

were posed to the investigator and the investigator responded.' The final consent form, dated 2 February 2001 reflected the concerns."

(b) With regard to protocol # HSC 01-18, the informed consent document approved by the UA IRB on February 13, 2001 stated the following:

(i) "**Risks:**

Also, the following flu-like symptoms (2%) have been reported by other study patients using imiquimod or placebo cream: fever, chills, muscle aches, bone aches, headaches, nausea, and/or fatigue."

(ii) "**Biopsy and Excision:**

It may be necessary to remove a larger area than the original lesion appeared for the excision so to ensure that all of the tumor is removed. Stitches will be used to close the wound.... The site will heal with a scar larger than one that is seen with either curettage and electrodesiccation or cryotherapy."

(c) With regard to protocol # 01-64, the informed consent document approved by the UA IRB on February 13, 2001 stated the following:

(i) "**STANDARD TREATMENTS**

The FDA approved standard treatment for metastatic malignant melanoma to lymph glands, [*sic*] which have been removed surgically is designed to prevent recurrence of disease or spread to other sites. The standard treatment is interferon alpha-2b which is given into a vein 5 days a week for 4 weeks followed by injection under the skin 3 times a week for 48 weeks. All other therapies to prevent recurrence of malignant melanoma are experimental at this time. They consist of other vaccines or chemotherapy plus interferon and IL-2. My physician will explain all of these to me."

(ii) "**RISKS**

My participation in this study involves some risks. The main side

> effects of the vaccine therapy are local skin reactions due to the administration of the vaccine/BCG combination in all patients.... Rarely, in less than 5% of the cases there may be fever, muscle aches and pains, skin rash, itching and there may also be redness and swelling near the site where I had the surgery. There is also a theoretical possibility that new tumor cells [*sic*] The cyclo-phosphamide treatment which is given only once causes nausea in about 25% of patients. This is usually prevented by anti-nausea medication. could grow under my skin as a result of the injection of the vaccine.[*sic*] This has never been observed in any of the 350 patients previously treated with the vaccine."
>
> "The side effects from the interferon, which is FDA approved for melanoma and are well documented in previous studies.[*sic*] The main side effects that I am likely to get is [*sic*] flu-like symptoms, upset stomach, diarrhea, depression, hair loss, which has [*sic*] occurred between 30 and 80% of patients receiving this treatment. Less than 5% of patients also report local reaction at the interferon injection site. Patients may also experience decrease in white blood cells, red blood cells or platelets and these decreases in these blood counts may require that the treatment may be interrupted and the dose reduced. In addition, some patients will have changes in liver function studies indicating liver damage. If this occurs, my treatment with the interferon will be stopped and the dose reduced. Rarely patients may have damage to the nerves in the hands and feet resulting in numbness and tingling. This usually reverses when the drug is stopped."

(iii) "**BENEFITS**

> Interferon treatment is reported to reduce the relapse rate in patients with my stage of melanoma by about 35%. The potential benefit of the vaccine is not known or proven. Neither interferon nor the vaccine may benefit me as an individual patient."

Based on (3)(a) and (b) above and OHRP's review of other information presented in your report, OHRP finds that the allegation that the informed consent document for protocol HSC # 01-18 failed to include the risks of scarring and flu-like symptoms was not substantiated. Based on (3)(a) and (c) above, OHRP finds that the allegation that the informed consent document for protocol HSC # 01-64 failed to include an adequate

description of the risks of the study was not substantiated. OHRP notes that the misalignment of the sentence regarding the theoretical possibility of the growth of new tumor cells in paragraph (3)(c)(ii) above affects the clarity of the presented information. The IRB should ensure that the proposed informed consent document is reviewed for errors that may impede a subject's understanding of the information.

(4) HHS regulations at 45 CFR 46.107(a) require that each IRB shall be composed of members possessing the professional competence necessary to review specific research activities. It was alleged that the UA IRB members did not have sufficient training or experience in the design and conduct of clinical studies to adequately assess the safety of the above-referenced research studies.

UA's November 4, 2003 Panel summary report stated the following in response:

> "The Panel found that the qualifications based on experience and expertise of each IRB member to be [*sic*] appropriate and completely within the [45] CFR 46.107 guidelines."

Based on a review of the qualifications of the IRB members that participated in the review of protocols # HSC 01-18 and # HSC 01-64 and OHRP's review of other information presented in your report, OHRP finds that the above allegation was not substantiated.

At this time, OHRP would like to provide the following guidance:

(5) Convened IRBs often set conditions under which a protocol can be approved. OHRP recommends the following guidelines in such cases:

> (a) When the convened IRB requests substantive clarifications or modifications regarding the protocol or informed consent documents that are directly relevant to the determinations required by the IRB under HHS regulations at 45 CFR 46.111, IRB approval of the proposed research should be **deferred** pending subsequent review by the convened IRB of responsive material.
>
> (b) Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator may the IRB chair or another IRB member designated by the chair subsequently approve the revised research protocol on behalf of the IRB under the expedited review procedure.

(6) Written IRB policies and procedures should adequately describe the procedures for prompt reporting to the IRB, appropriate institutional officials, the department or agency

head, and OHRP of: (i) any unanticipated problems involving risks to subjects or others; or (ii) any serious or continuing noncompliance with 45 CFR part 46 or the requirements or

determinations of the IRB, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

OHRP appreciates the commitment of UA to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Robert J. Meyer
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Rebecca W. Dahl, Director, Human Subjects Protection Program, UA
Dr. David G. Johnson, Chair, UA IRB #1 & #3
Dr. Theodore J. Glattke, Chair, UA IRB #2
Dr. Evan Hersh, UA
Dr. Norman Levine, UA
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