DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

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Warning Letter

Lyman H. Harris, Esq., Chairman
ImmunoGenetics Investigational Review Board
Harris, Cleckler & Hollis, P.C.
2007 Third Avenue North
Birmingham, Alabama 35203-3347

Dear Mr. Harris

From June 15 to July 9, 2001, Ms. Patricia Smith, an investigator with the Food and Drug Administration (FDA), inspected the ImmunoGenetics Investigational Review Board that serves as an Institutional Review Board (IRB). The purpose of this inspection was to determine if the IRB's procedures for the protection of human subjects comply with FDA regulations, published in Title 21, Code of Federal Regulations, Parts 50 and 56 [21 CFR 50 and 56].

The IRB was constituted to review the study titled [illegible] All study-specific observations listed in this letter relate to this study.

We enclose a copy of the list of Inspectional Observations (Form FDA 483) presented in your absence to Mr. Brock Murphy, IRB Secretary, at the end of the inspection. The inspection noted the following deficiencies:

1 **Failure to prepare detailed written procedures for conducting the review of research, including periodic review. [21 CFR §§ 56.108(a), 56.115(a)(6)].**

A. **There are no written instructions as to how the IRB is to operate.**

The regulations require that the IRB shall adopt and follow written procedures for conducting its review of research. The procedures should describe the following:

- IRB organization
- how many voting members make up the IRB
- how IRB members are selected
- explicitly outline how applications are processed
- who will receive pre-meeting materials to review
- how the review is to be conducted

how decisions are made
how controverted issues are decided
what criteria are used to determine the basis of approval of research proposals
the frequency of continuing review
how records must be maintained to fulfill federal requirements
how the IRB will consider research proposed by IRB members
how the IRB will avoid conflict of interest in its reviews
how the IRB will ensure prompt reporting to the IRB of changes in research activity and that changes will not be initiated without IRB review and approval

Written procedures should describe in detail the following aspects of IRB continuing review operations:

- how and when renewal notices are sent to clinical investigators
- how administrative staff processes interim reports
- how periodic reports are discussed
- the voting method the IRB will use for continuing reviews
- how the IRB will follow-up in the event of a lack of response or an incomplete response
- how the IRB will document its actions for ensuring that progress reports are submitted and reviewed at the specified time intervals
- the content of progress reports should be described in detail so that clinical investigators will provide the IRB with interpretable periodic reports.

B. **There are no written procedures to describe how the IRB will determine when an investigation involves an investigational product subject to FDA regulation.**

The IRB did not request information to determine whether research involves a product regulated by FDA, and the investigational new drug application (IND) or investigational device exemption (IDE) number associated with the investigational drug, biologic, or device. An IND was not submitted for [redacted] study until approximately three years after the research was initiated. The IRB should have a mechanism in place to contact FDA to discuss proposed research if the IRB is unsure whether an IND or IDE is required. The IRB should not rely solely on a clinical investigator's interpretation of FDA requirements.

C. There are no written procedures to describe how the IRB will determine when an investigation involves a significant risk device.

D There are no written procedures for incorporating revisions to proposed research and for notifying the full IRB of those revisions. Written procedures should describe how the IRB will assure that studies "approved" pending modifications are not initiated before the IRB accepts the modified documents.

E There are no written procedures to describe the extent to which the IRB will review advertisements for studies approved by the IRB. Information on web sites is considered advertising.

F There are no written procedures to describe how adverse reaction reports are reviewed, by an "expedited" process or by the full IRB.

G There are no written procedures to explain the role of the IRB Chair, and who performs those functions when the Chair is absent. The IRB's meeting minutes document that the Chair has not attended the majority of IRB meetings, and none since May, 1999.

H There are no written procedures for ensuring prompt reporting to the appropriate institution officials and FDA of the following:

Any unanticipated problems involving risks to human subjects or others.

ii. Any instance of serious or continuing noncompliance with FDA regulations or the requirements or determinations of the IRB.

iii. Any suspension or termination of IRB approval

There are no written procedures to describe how the IRB will review proposed research and proposed informed consent documents for information regarding the charging of study subjects for investigational products under FDA jurisdiction.

The information should also be provided to clinical investigators. FDA prohibits charging for investigational drugs and biologics unless specifically approved with the limitations described in 21 CFR § 312.7. The limitations for charging for investigational devices are described in 21 CFR § 812.7.

2. Failure to review research. [21 CFR § 56.109(a)].

A. On July 9, 1997, the IRB conditionally approved the study without reviewing a written protocol. There is no documentation that the IRB reviewed the study design, inclusion/exclusion criteria, and study

procedures to ensure that the study did not needlessly expose study subjects to risk. The complexities of the study cannot be fully considered based on an oral presentation at a meeting without prior review of the written study proposal. The conditional approval was based on the IRB's requirement for "preparation of an appropriate Informed Consent Form" prior to beginning the study. See item 4A, below.

B The IRB failed to determine the frequency at which periodic review would be conducted for the study.

C. At the meeting held May 7, 1999, the IRB approved an unwritten protocol revision permitting ———— to manufacture ———————— using frozen ———— tissue obtained from a deceased person. In the absence of a detailed written proposal, it was not possible for the IRB to fully assess the adequacy of the proposal's provisions to protect study subjects from the increased risks inherent in transfer of transplanted tissue or tissue components. The IRB failed to consider whether the manufacturing process was adequate to remove adventitious agents. Furthermore, there was no scientific discussion as to whether there was a possibility that the another person's tumor tissue could produce an immunologic tumoricidal response in another person. See items 3B and 5A, below.

3. Failure to require that information given to subjects as part of informed consent is in accordance with the provisions of 21 CFR § 50.25. [21 CFR § 56.109(b)]

A. The IRB failed to review the informed consent documents for the study. ———— discussed the existence of two informed consent documents during the IRB meeting held May 20, 1998, yet there is no documentation that the IRB obtained the documents, reviewed or approved them.

B The IRB failed to require that ———— prepare/revise the informed consent documents to described the additional risks from receiving a vaccine manufactured from tumor tissue obtained from a different person. There is no documentation that the IRB determined that potential study subjects should be informed that this protocol modification exposed the subject to additional risks.

4. Failure to ensure that changes in approved research are not initiated without IRB review and approval. [21 CFR § 56.108(a)(4)].

A. The IRB conditionally approved the study on July 9, 1997, based on the requirement for preparation of an informed consent document prior to beginning the study. The IRB did not follow up to ensure that ————

submitted and received IRB approval of informed consent documents before he obtained blood and tumor tissue samples and initiated the study.

B. At the IRB meeting held on May 20, 1998, ——— reported that he had administered the investigational ——— to five subjects even though the IRB had granted only a conditional approval at the previous meeting. The conditional approval was based on the IRB's requirement for "preparation of an appropriate Informed Consent Form" prior to beginning the study. Furthermore, the meeting minutes report that subject #1 "signed an informed consent form" even though the IRB had not reviewed or approved any informed consent documents. There is no documentation that the IRB took action to prohibit further enrollment until an informed consent document was reviewed and approved. See also items 2A, above, and 11D, below.

C. At the IRB meetings held May 20, 1998, and January 28, 1999, ——— reported that he had administered the investigational ——— to four subjects who had cancers other than ——— The IRB had conditionally approved the study for ——— at the IRB meeting held July 9, 1997. There is no documentation that the IRB questioned ——— or took corrective action regarding his decision to violate the protocol by enrolling subjects with ———

D. At the IRB meeting held on May 20, 1998, ——— reported that he had administered two different ——— on the same day to subject #4 . He modified the manufacturing method without obtaining prior IRB approval. There is no documentation that the IRB questioned ——— regarding his decision to alter the manufacturing process without prior IRB approval. There is no documentation that the IRB requested information about how the manufacturing change affected risks to subjects. The meeting minutes report that the ——— technique" was then used "for his other patients."

5. Failure to fulfill membership requirements. [21 CFR § 56.107(a)].

A. The IRB membership does not include an adequate number of members who possess the professional competence necessary to review the specific research activities. For example, the IRB membership appears to lack the scientific expertise to assess the manufacturing procedures and to recognize that ——— exposed subjects to additional risks by administering a ——— manufactured from ——— tissue to a different subject with a ——— See item 2C, above.

B. The IRB lacks members with the expertise to be able to ascertain the acceptability of proposed research in terms of applicable law and standards of professional conduct and practice. The IRB appears to lack personnel who are knowledgeable about FDA requirements and who can distinguish when proposed research must be performed under an IND or IDE.

C. Prior to the meeting held on January 11, 2001, the IRB membership included only one physician/scientific member, ——— (with the exception of . ——— presence at a single meeting; see item 6Aii, below).

6. **Failure to insure that research is reviewed free from conflict of interest. [21 CFR § 56.107(e)]**

A. IRB members did not always exclude themselves from deliberation and voting on their own research projects and on projects for which they have a conflict of interest. The following examples are not a complete list:

——— is a voting member of the IRB and was formerly ——— secretary. The IRB member roster identifies her address as that of ——— medical office. ——— current or former employment by the clinical investigator creates a connection to the clinical investigator that could influence her consideration of proposed research.

——— participated as a voting member during the IRB meeting held February 11, 1999 ——— is identified as a subinvestigator participating in the study and, therefore, is not permitted to vote on matters regarding ——— study due to a conflict of interest.

B The IRB has not determined or documented whether any IRB member has a financial interest in the institution ImmunoGenetics, Inc.

We note that the clinical investigator personally recruited several of the IRB members with whom he had a personal or professional relationship. The presence of these IRB members gives an impression that the deliberations might not be impartial to the clinical investigator. Furthermore, most IRB meetings took place in the clinical investigator's office, which gives an impression that the deliberations concerning the research might not be impartial to the clinical investigator and/or the research.

7. Failure to exercise authority to require modification in (to secure approval) or disapprove all research activities covered by these regulations. [21 CFR § 56.109(a)]

A. The IRB did not assure that studies subject to FDA regulation are conducted under an IND or IDE. Research that is subject to FDA oversight must be performed under an effective IND or IDE, unless the IRB determines that a device study poses a non-significant risk. In instances when an IND or IDE is necessary, the IRB should not approve research in the absence of an IND or IDE. See items 1B and 5B, above.

B. The IRB did not review the proposed research to assess whether the study involves charging subjects for investigational products under FDA jurisdiction. For example, the minutes for the IRB meeting held November 22, 1999, report that a subject's "wife paid approximately $5000 to cover the costs of the creation of this ——— See item 1I, above.

8. Failure to review proposed research at convened meetings at which a majority of the members of the IRB are present, and include members with primary concerns in scientific areas. [21 CFR § 56.108(c)].

A. There was neither a physician member, a scientific member, nor a quorum of the IRB members present during the meeting held May 7, 1999, when the IRB approved ——— request to change the protocol to permit the use of a deceased person's——— cells to produce ——— for a new subject. The IRB permitted this protocol revision without reviewing a written protocol modification. See item 2C, above.

B. There was no physician member present at the IRB meeting held on January 11, 2001, when the IRB approved "to issue a pro-active approval for the receipt...of a compassionate use exemption" for two subjects who were enrolled before the IND was submitted to FDA.

9. Failure to notify investigators in writing of its decision to approve or disapprove the proposed research activity, or of the modifications required to secure IRB approval of the research activity. [21 CFR § 56.109(e)].

There is no documentation that the IRB notified the clinical investigator in writing of the IRB's decision to approve or disapprove research, the frequency of continuing review, and the results of the IRB's continuing reviews of the study.

10. Failure to conduct continuing review of research. [21 CFR § 56.109(f)].

During the IRB meeting held on January 28, 1999, ———— reported that two subjects had experienced systemic adverse events following the administration of the investigational product. The events included "flu-like aches all over their body, and weakness...had trouble walking...aches were noted within the joints." ———— described these reactions as an indication that the investigational regimen was effective. Previously, during the IRB meeting held on May 20, 1998, ———— reported "no side effects from this treatment regimen." Furthermore, these adverse events were not reported at the IRB meeting held on January 11, 1999, when a quorum of members was present. In the absence of a written progress report to the IRB, the IRB failed to conduct adequate continuing review.

11. Failure to have procedures to determine that risks to subjects are minimized. [21 CFR § 56.111].

A. The IRB approved the study without reviewing a written protocol. There is no documentation that the IRB discussed the study design, inclusion/exclusion criteria, and study procedures to prevent unnecessary exposure to risk.

B The IRB approved the study without assessing whether selection of subjects is equitable.

C. The IRB approved the study without assessing whether the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

D. During the IRB's first convened meeting on July 9, 1997, the IRB conditionally approved the study without reviewing an informed consent document. By the time of the second convened IRB meeting on May 20, 1998, five subjects had been enrolled in the study, yet there is no record that the IRB had reviewed the informed consent document and fully approved the study. The IRB failed to ensure that ———— made all IRB-required modifications prior to enrollment of research subjects.

E. There is no documentation that the IRB assured there are adequate provisions to protect the privacy of subjects to maintain confidentiality of data.

F. There is no documentation that the IRB assured that additional safeguards are in place to protect the rights and welfare of subjects such as children, mentally disabled, economically disadvantaged, or educationally disadvantaged persons who are likely to be vulnerable to coercion or undue influence.

12. Failure to prepare adequate documentation of IRB activities. [21 CFR § 56.115]

FDA believes that the records that an IRB or an institution must maintain provide significant evidence of whether the procedures utilized by the IRB are adequately protecting the human subjects of the investigations that the IRB is reviewing. The IRB failed to prepare or maintain the following records:

A. Copies of the research protocols reviewed, scientific evaluations, if any, that accompany the protocols, approved informed consent documents, progress reports submitted by the clinical investigators, and reports of injuries to subjects. These examples are not a complete list:

The IRB did not have a copy of any version of the protocol. In fact, the first record of the study's title is in a document dated February, 2000, more than 30 months after the beginning of the study.

ii The IRB did not have a copy of the informed consent documents, even though the minutes for the IRB meeting held May 20, 1998, record that the IRB reviewed two informed consent documents and suggested certain changes.

B Minutes of IRB meetings documenting actions taken by the IRB, the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution. These examples are not a complete list:

The meeting minutes do not document whether the IRB determined the frequency with which continuing review must be conducted on ———— study.

ii. The meeting minutes do not report whether or not the clinical investigator left the room during IRB deliberations and voting on the study.

iii. The minutes for the meeting held May 20, 1998, state that one member "suggested certain changes" to an informed consent document, yet the changes are not specified.

iv. The meeting minutes do not document whether the IRB deliberated charging subjects for study-related costs.

C. Records of continuing review activities. There is no record that ——— submitted written progress reports or supporting documents for IRB review, and no record of the intervals at which progress reports were required.

D. Copies of all correspondence between the IRB and the investigator. There is no documentation that the IRB reported its findings and actions to the clinical investigator.

E During the inspection, there was no available list of IRB members identified by name that includes earned degrees, representative capacity, indications of experience such as board certifications, licenses, etc sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution.

F. Written procedures for the IRB; see item 1, above.

G There is no documentation whether the IRB reviewed or approved the web site advertising for ——— ; study.

This letter is not intended to be an all-inclusive list of deficiencies.

Based on the deficiencies found during this inspection, we have no assurance that your IRB procedures are adequately protecting the rights and welfare of the human subjects of research. *For this reason, in accordance with 21 CFR 56.120(b)(1) and (2), and effective immediately,*

- ***no new studies*** *that are subject to Parts 50 and 56 of the FDA regulations are to be approved by your IRB, and*

- ***no new subjects*** *are to be admitted to ongoing studies that are subject to 21 CFR Parts 50 and 56 until you have received notification from this office that adequate corrections have been made.*

These restrictions do not relieve the IRB of its responsibility for receiving and reacting to reports of unexpected and serious reactions and routine progress reports from ongoing studies.

Please notify this office in writing, within fifteen (15) business days of receipt of this letter, of the actions you have taken or plan to take to bring the procedures of your IRB into compliance with FDA requirements. Please include a copy of any revised documents, such as written procedures, with your response. Any plans of action must include projected completion dates for each action to be accomplished. In addition, please submit a copy of the written notification from the IRB to each of the affected clinical investigators notifying them of this suspension.

We will review your response and determine whether the actions are adequate to permit the IRB to resume unrestricted activities. Your failure to adequately respond to this letter may result in further administrative actions against your IRB, as authorized by 21 CFR 56.120 and 56.121. These actions include, but are not limited to, the termination of all ongoing studies approved by your IRB and the initiation of regulatory proceedings for disqualification of your IRB.

Your written response should be addressed to:

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Sincerely,

Steven A. Masiello
Director
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Center for Biologics Evaluation and Research

Enclosure
Form FDA 483

cc: Brock G. Murphy, Esq., Secretary
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