DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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By Certified Mail - Return Receipt Requested

CBER--02-- 005

Warning Letter

DEC 11 2001

R. Cem Cezayirli, M.D.
Haynes Neurosurgical Group, P.A.
801 Princeton Avenue, S.W., Suite 310
Birmingham, Alabama 35211

Dear Dr. Cezayirli:

During an inspection that ended on October 3, 2001, Ms. Patricia Smith, an investigator from the Food and Drug Administration (FDA), visited your office to examine records relating to your clinical study of an investigational activated cell product. The title of the study is "Autologous Programmable Dendritic Cell Vaccine." This letter addresses your duties as both the sponsor of the research and the clinical investigator responsible for the enrollment and administration of the investigational activated cell product to human subjects. The inspection is part of FDA's Bioresearch Monitoring Program that includes inspections designed to review the conduct of research involving investigational new drugs.

The inspection also included a review of your study of an investigational medical device. The inspectional findings from the device study are discussed later in this letter.

It bears noting that the inspection revealed information about your use of the investigational activated cell product during the period from 1997 through [redacted], before you submitted the [redacted] Investigational New Drug Applications (INDs) to FDA. Our comments on your research during that period are listed on pages three to five of this letter.

We determined that during the period since [redacted], you violated regulations governing the proper conduct of clinical studies involving investigational new drugs as published under Title 21, Code of Federal Regulations (CFR), Part 312 available at http://www.access.gpo.gov/nara/cfr/index.html . The applicable provisions of the CFR are cited for each violation listed below.

1. **You failed to permit an FDA officer to have access to and copy and verify records and reports relating to a clinical investigation conducted under Part 312. [21 CFR § 312.58(a)].**

   a. During the inspection you refused to identify the name(s) or location(s) of laboratory (ies) manufacturing the investigational activated cell product. In the INDs you submitted to FDA in [redacted], you state that the laboratory facilities are located in the same building as your office, yet the inspection revealed that your laboratory was converted into office space in [redacted], one year before you submitted the first IND to FDA.

b. You failed to provide access to the records for each subject you described in your Investigational New Drug Applications (INDs). You submitted summaries of these subjects to the INDs as required by 21 CFR § 312.23(a)(3)(ii) to describe the previous human experience with your proposed investigational activated cell product. Yet, during the inspection you were unable or refused to provide the medical records of one subject for verification and copying, and of two subjects for copying. The protocol assures FDA that "the informed consent documents, patient histories, and records of vaccination and outcome will be handled and stored within the office suite of Haynes Neurosurgical Group P.A."

c. By your own admission, you initiated the protocol for "maybe six" new subjects outside the U.S. after you became aware that the study must be conducted under an IND, yet you declined to identify or provide records for these subjects.

2. **You failed to withhold administration of an investigational new drug until an IND is in effect. [21 CFR §§ 312.20, 312.40(d), and 312.50].**

You administered the investigational activated cell products to subjects [redacted] and [redacted] in the [redacted] when there was no IND in effect even though you were aware that an IND was required to conduct the research. You submitted your first IND to FDA in [redacted]. In [redacted] You administered the product to subject [redacted] in July 2000, and to subject [redacted] in October and November 2000, without having an IND in effect. See also item 1C above.

3. **You are promoting investigational drugs in violation of 21 CFR § 312.7(a).**

Sponsors may not represent in a promotional context that an investigational new drug is safe or effective for the uses that are under investigation. Your website at http://www.immuno-genetics.com is promoting your study and contains the following examples of therapeutic and safety claims about your study:

> "Years of research have developed a unique procedure with the use of Dendritic cells that provides a cure through arousing the body's own immune system to respond to cancer that has normally been effective in hiding from the body's immune system."
> "This patented procedure will detect and destroy the majority of cancer types using natural methods that produce no side harmful effects."

"As you can see from our survivors page, we have had good success with some of the worst tumors known to man. Basically, of the 3 original patients that we treated more than 3 years ago, 2 are still alive and well." This statement is misleading because it fails to describe that several other subjects died while participating in the research.

Comments on your research during the period from 1997 until [redacted]
During the period from 1997 to [redacted], before you submitted an Investigational New Drug Application (IND) to FDA, you were responsible for the following conduct:

1. You charged the subjects money for the investigational activated cell product.

   Please note that charging for an investigational drug under an IND is not permitted without the prior written approval of FDA under 21 CFR § 312.7(d).

2. You failed to maintain adequate case histories of individuals treated with the investigational activated cell product, including the number of cells administered to each injection site for each subject.

3. You improperly used the Baptist Medical Center form entitled "Consent to Operation or Other Procedure" to obtain consent from subject [redacted] for the procedure "Dendritic Cell Vaccine." On July 27, 1999, you performed surgical debulking of subject [redacted] tumor at Baptist Medical Center. On August 7, 1999, after the surgery, subject [redacted] signed the consent form. You administered the vaccine to subject [redacted] on August 7, 1999, and August 24, 1999.

   This is an improper use of the institution's form because it implied to the subject that the institution had approved the research. You did not have the institution's approval to conduct the research. The Baptist Health System Institutional Review Board (IRB) informed you on [redacted], that you were not permitted to involve the institution in the research without full review and approval by the IRB.

4. The consent forms you submitted to FDA in [redacted] are misleading because they imply that the Baptist Health System is a willing participant in the research. As described in item C above, at the time you submitted the INDs you did not have IRB approval to conduct any aspect of this study at that institution.

5. You failed to provide a copy of the protocol to the ImmunoGenetics' Investigational Review Board during their review of your study, citing concerns about proprietary information.

6. You failed to obtain IRB approval of at least four different consent forms utilized in your clinical study. Neither the ImmunoGenetics' IRB nor the Baptist Health Systems IRB reviewed and approved the consent forms listed below. In additional, none of the following consent forms contain the elements of informed consent required by 21 CFR § 50.25:

   a. The consent form entitled "Vaccine Consent Form " that was signed by subjects [redacted]

   b. The consent form entitled "Brain Tumor Study Immunogenetics Patient Consent Form" that was signed by subjects [redacted]

   c. The consent form entitled "Consent to Operation or Other Procedure" that was signed by subject [redacted]; see item D above.

   d. The consent form that was signed by subject [redacted] that released you and ImmunoGenetics, Inc. from any consequences of drawing blood, and from any future claims for the blood or related products in the future.

7. You enrolled subjects who did not have brain tumors, and therefore were not eligible to participate according to the study concept conditionally approved by the ImmunoGenetics' Investigational Review Board meeting held [redacted]. In the IND you submitted to FDA in [redacted], you report that you administered the activated cell product to subjects with other neoplasms, including osteosarcoma, colorectal cancer, and neurofibrosarcoma.

8. You used a brain tumor extract from a deceased subject to manufacture the investigational activated cell product for another subject. During the inspection you acknowledged that the use of another person's tumor tissue would result in risk to subjects. There are no records that you performed any quality control testing to detect and prevent the transmission of adventitious agents from the deceased subject to this immunosuppressed recipient.

   Although you included this subject's medical history in the INDs submitted to FDA in [redacted], we note that you failed to report to FDA that this subject received cells activated with an allogeneic tumor extract.

9. During the inspection you stated that you have never seen the laboratory (ies) where the investigational activated cell product has been manufactured since [redacted]. You stated that you have no records to document how the investigational activated cell product was/is manufactured, or that quality control testing was/is performed.

In the INDs you identified several steps in the manufacture of the investigational activated cell product, yet you cannot document that the product was adequately or consistently manufactured, and that the investigational activated cells were viable and sterile at the time of injection.

In addition to the serious deficiencies associated with the investigational new drug studies you conducted, there were deficiencies associated with your conduct of an investigational device study entitled, [redacted] The Investigational Plan for the Pivotal Trial of the [redacted] Study Indication: [redacted] The study was sponsored by [redacted] to investigate the device [redacted], in support of the [redacted] investigational device exemption (IDE) application, [redacted] You failed to adhere to the specific responsibilities of investigators in that you did not have IRB approval between [redacted], yet you continued to conduct research activities associated with the [redacted] You failed to maintain study subject source documents relating to the [redacted] investigation and complete records relating to your participation in an investigation. You failed to conduct the investigation in accordance with the investigational plan. For example, the study protocol for the [redacted] study requires placement of heparin (1-2 ml) into the sterile bowl containing the bone marrow aspirate to prevent the bone marrow aspirate from clotting. This procedure was not performed for some study subjects.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of investigational drugs. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

Please notify us, in writing, within fifteen (15) business days after receipt of this letter, of the steps you have taken or will take to correct the noted violations. If corrective actions cannot be completed within fifteen (15) business days, state the reason for the delay and the time within which the corrections will be completed. This letter does not preclude the possibility of a corollary judicial proceeding or administrative action concerning these violations.

Failure to achieve correction may result in enforcement action without further notice. The actions could include termination of your IND, initiation of disqualification proceedings which may render a clinical investigator ineligible to receive investigational new drugs and devices, and/or injunction.

Please send your written response to:

Patricia Holobaugh (HFM-664)
Division of Inspections and Surveillance
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 29852-1448
Telephone: (301) 827-6221

Viola Sellman (HFZ-312)
Chief, Program
Enforcement Branch II
Office of Compliance
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850
301) 594-4723 ext. 127

We request that you send a copy of your response to the following Food and Drug Administration offices:

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Food and Drug Administration
6600 Plaza Drive, Suite 400
New Orleans, Louisiana 70127

Howard E. Lewis
Branch Director
Food and Drug Administration
297 Plus Park Boulevard,
Suite 100
Nashville, Tennessee 37217

Sincerely yours,

Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation
and Research

Clarence Connor, RPh, RAC
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Director
Office of Compliance
Center for Devices and
Radiological Health

cc: Dr. John A. Pinkston, Chairman
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Baptist Health System, Incorporated
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