DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

By Certified Mail - Return Receipt Requested

NOV 1 2002

NOTICE OF OPPORTUNITY FOR HEARING

Peter K. Law, Ph.D.

[redacted]

Dear Dr. Law:

The Food and Drug Administration (FDA, the agency) has information indicating that you repeatedly or deliberately violated Federal regulations in your capacity as investigator in clinical trials with the unlicensed biological and investigational new drug, Myoblast Transfer Therapy (MTT). These violations provide the basis for the withdrawal of your eligibility as a clinical investigator to receive investigational new drugs.

By letters dated June 30, 2000, and August 17, 2001, the Center for Biologics Evaluation and Research (CBER) informed you of the specific matters complained of and offered you the opportunities to respond to them in writing or at an informal conference pursuant to §312.70(a) of Title 21 of the Code of Federal Regulations (CFR). The letters also gave you the option of entering into a consent agreement with the agency, thereby terminating any administrative proceeding against you. You chose to respond in writing, in letters dated September 6, 2000, December 20, 2000, and October 2, 2001, transmitted through your attorney, [redacted]. CBER has concluded that your written explanations fail to adequately address the violations set forth below. Accordingly, you are being offered an opportunity for a regulatory hearing pursuant to 21 CFR Part 16 and 312.70, on the question of whether you are entitled to receive investigational drugs. You have the right to be advised and represented by counsel at all times. Any regulatory hearing on this matter will be governed by the regulations in 21 CFR Part 16, and the FDA's guidelines on electronic media coverage of public administrative proceedings, 21 CFR Part 10, Subpart C. Copies of those regulations are enclosed.

The allegations involve the following clinical studies in which you are the clinical investigator of record:

> Protocol 93-5 - "Myoblast Transfer Therapy as an Experimental Treatment for Duchenne Muscular Dystrophy;"

Protocol 95-1 - "Whole Body Myoblast Transfer Therapy (MTT) as an Experimental Treatment for Duchenne Muscular Dystrophy (DMD) – Pivotal Trial;"

Protocol 95-2 - "Whole Body Myoblast Transfer Therapy as an Experimental Treatment for Becker Muscular Dystrophy;"

A listing of the specific violations follows. These are the matters that will be considered at a regulatory hearing. Applicable provisions of the CFR are cited for each violation.

1. **You failed to fulfill the general responsibilities of an investigator. [21 CFR § 312.60].**

As the clinical investigator of record, you are responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and the applicable regulations; for protecting the rights, safety, and welfare of your study subjects; and for the control of drugs under investigation. On ————, you signed an FDA Form 1572 Statement of Investigator, in which you agreed to fulfill the requirements regarding the obligations as a clinical investigator and all other pertinent requirements in 21 CFR Part 312.

You failed to fulfill your obligations as the clinical investigator in the following manner:

A. You failed to protect the rights of study subjects. See item 3 below.

B. You failed to adequately protect the safety and welfare of study subjects.

i. You permitted study staff to perform study functions even though they did not possess appropriate medical licensing credentials. You permitted ————, M.D. to perform study tasks that required the expertise of a licensed physician even though he was not a licensed physician in Tennessee. You permitted Dr. ———— to adjust the dosage of cyclosporine for study subjects, and to conduct medical chart reviews in order to make medical judgments as to whether subjects were fit to undergo the experimental procedure. You relied on Dr.———— to determine whether potential donors were medically fit to undergo tissue donation, and, in some cases, evidence indicates he accepted ineligible donors for tissue donation (see also item 2G, below). Furthermore, you utilized Dr. ————to make assessments about the relationship of adverse events to the investigational product even though he is not qualified to do so, and he accepted donors with abnormal laboratory tests.

Your response letter dated September 6, 2000, claims that FDA was aware of the manner in which potential study subjects and donors were screened, evaluated, and enrolled into the study, and that FDA did not object to your practices as a clinical investigator. On the contrary, FDA was not aware that you delegated medical decision making to individuals who were not qualified to make medical decisions. Your argument that FDA did not object to practices it was not aware must fail.

ii. The available records do not identify the licensed physician who initially prescribed and determined the proper dosage of cyclosporine for each subject, and who was responsible for monitoring the toxicity of this drug in the subjects. See item 5B below.

C. You failed to follow the investigational plan. See item 2 below.

2. **You failed to conduct the studies in accordance with the approved protocols. [21 CFR § 312.60].**

A. You did not provide adequate oversight to assure that subjects maintained the protocol-specified blood levels of cyclosporine. Some subjects were rarely tested to determine the levels resulting from their cyclosporine doses. Some subjects' blood levels were significantly above the protocol specified range of ———— ng/ml. For example, records indicate subject —— enrolled in protocol # 95-2 had cyclosporine levels of 473 ng/ml before the MTT procedure was performed, and at other times had the levels ranging from 401 to 626 ng/ml.

Furthermore, Subject — was not adequately monitored by you for adherence to the protocol and cyclosporine levels were not regularly measured. Without your knowledge, subject — abruptly stopped taking cyclosporine several weeks before the time specified in the protocol. See item 3C below.

In your response letter dated September 6, 2000, you state "cyclosporine levels were monitored by subjects' individual physicians. Either individual physicians adjusted dosages or test results were sent to CTRF [Cell Therapy Research Foundation], where a physician adjusted dosages." However, there is no documentation that the subjects' individual physicians adjusted the cyclosporine dosage. In fact, your response contradicts the information presented in the "Parents' Pak", which states in part:

> Laboratory tests are extremely important to monitoring your health. This test ensures that you are having no problems, either from the transplant or the cyclosporine. Tests will be conducted before, during, and after transplant. From the results of the tests, Foundation doctors will recommend changes in cyclosporine doses. We will often contact you to verify changes in dose. It is important that you keep an accurate log of your doses.

Your response letter dated September 6, 2000, acknowledges that the desired cyclosporine serum level requires adjustment of each subjects' cyclosporine dose, yet you failed to implement and document that such adjustments were made. The response also states:

> ...in some instances, cyclosporine serum levels were performed less frequently than required by the study protocols. This occurred because the subjects' parents did not adhere to the specified schedules, sometimes for reasons beyond their control. A number of the non-U.S. subjects, for example, live in countries where access to health care facilities is limited or where similar barriers to medical care exist.

We reject your explanation. Subjects' files document that study personnel were aware that cyclosporine testing was infrequently performed for some subjects, yet you did not require compliance with the protocol and simply ignored this protocol requirement. You enrolled subjects from other countries where it was questionable as to whether the subjects would be able to obtain these important tests. Your recruitment of subjects without access to adequate health care facilities was a deliberate failure to follow the protocol. The subjects you describe constitute vulnerable populations whose special problems of research should have been carefully considered. See item 3A below.

B. You failed to comply with the exclusion criteria for donors in protocol 95-1. You permitted at least 3 donors (————————) to donate muscle tissue even though their levels of creatine kinase exceeded the protocol required limits.

In your response dated September 6, 2000, you attribute the elevated creatine kinase levels to "intense exercise." The protocol does not provide for an exception even if the increased creatine kinase was due to "intense exercise." According to protocol requirements, these potential donors should have been deferred.

C. You did not retain a board-certified pulmonologist to review and evaluate the pulmonary function test results or subjects, as required by protocol 93-5.

Your response dated September 6, 2000, asserts that board-certified ———— , M.D., Ph.D., reviewed the pulmonary function testing. However, there is no documentation in the medical records or case report forms to verify that Dr. ———— actually reviewed and evaluated the records of these tests. We reject your explanation in the absence of documentation.

D. You enrolled subject ———— into protocol 93-5 without tests to confirm which form of muscular dystrophy affected him. DNA deletion analysis revealed that there were no detected DNA deletions.

In your response dated September 6, 2000, you state that the clinical diagnosis "eventually was confirmed," but you failed to provide such documentation with your response letter. The protocol did not permit you to enroll this subject in the absence of proper documentation that the subject was affected by Duchennes' muscular dystrophy.

E. Protocol 95-2 specified that only subjects with a diagnosis of Becker muscular dystrophy could be enrolled in this study. You enrolled subject — (# — who was affirmatively diagnosed to have the Limb-Girdle form of muscular dystrophy.

Your response letter dated December 20, 2000, acknowledges that subject —(# — has Limb-Girdle muscular dystrophy.

F. For subjects who received the ———————————— in protocol 93-5, there are no records to document the performance of the required ———— pulmonary function tests that were to be conducted for safety monitoring for —— months by each subject's local physician.

Your response dated September 6, 2000, acknowledges that this finding is correct.

G. You obtained muscle tissue from donors who failed to meet the age inclusion criterion requirement that donors for study 93-5 must be between ———— years old. The protocol states, " ⌊— —⌋ ⌊— —⌋ This following table is not a complete list.

Donor	Age of Donor	Recipient(s)	Consent Date
			6/12/95
			1/23/96
			10/17/95
			6/13/96
			5/22/96
			1/27/95
			8/6/96
			2/29/96
			5/1/96
			5/21/96
			6/13/96

Your response dated October 2, 2001, explains that "by 1995, the specification had been changed to permit an age range of —— " Although the new protocol for Study 95-1 (dated May 30, 1995) reflects the revised age range for acceptable donors, you failed to revise the protocol for Study 93-5 to permit the expanded age range. You were responsible for adhering to the IRB-approved protocol until such time as the IRB approved a protocol amendment for this change.

H. You enrolled subject —— who was CMV IgM positive, in violation of the exclusion criteria defined in protocol 93-5. Subject ICC had a CMV IgM level of 1.6. The laboratory report reads as follows: ">1.1 - positive. Either current or acute infection or recent infection probably occurred in the previous six months." As such, you exposed this subject to increased risk because, under your direction, the subject was immunosuppressed with cyclosporine as part of the protocol.

Your response dated October 2, 2001, failed to address this observation.

I. You failed to administer the number of myoblasts required by the protocols. The protocols specify the number of myoblasts required, not an acceptable range in the number of cells that could be administered. The following examples of subjects over-dosed or under-dosed are not a complete list.

Protocol	# Cells required by Protocol	# cells administered - subject	Date
93-5	———	——— - subject ——— ——— - subject ——— ——— - subject ——— ——— subject ——— ——— - subject ——— ——— - subject ———	9/10/96 2/29/96 4/20/95 10/27/94 9/26/95 2/7/96
95-1	———	——— - subject ———	6/6/96

In your response dated October 2. 2001, you attribute these protocol violations to "variation from the intended ingredient amounts." You also cite FDA "Guidance for Human Somatic Cell Therapy and Gene Therapy" (1998) to support your contention that the overdosing and underdosing of subjects is somehow acceptable. We do not agree that the total number of cells administered should vary from the amount specified in the protocol. Indeed, study personnel simply administered all the myoblasts that were harvested instead of administering solely the protocol-required number of cells.

J. Approximately ———of the myoblast cells injected into subject—— were harvested two days before the MTT procedure. Protocol 95-2 states, "the procedure for harvesting will be [redacted]" There is no documentation that harvested myoblasts retain their functionality if stored at——for——— before MTT.

Your response dated October 2, 2001, states that "immediately before the transplant was scheduled to take place" you determined that the subject might have a latex allergy, and that therefore the transplant was delayed so that the procedure could take place in a hospital.

We do not accept your explanation that performing a viability test was sufficient to permit this protocol violation. You argue that deviations are essential to eliminate possible hazards to the subject, but deviations without IRB approval are simple protocol violations. Furthermore, this example illustrates the safety problems that may be encountered by deferring a medical exam and review of the medical history by a physician until immediately prior to the investigational procedure. In the case of subject—— , you decided to begin harvesting the myoblast cells before the medical history and physician exam were conducted.

K. You failed to obtain the informed consent from the subject or subject's representative according to the schedule included in the approved protocols. The protocols require that the subject or the subject's representative sign the consent form ———— in advance of the MTT procedure. At least— subjects enrolled in protocols 93-5, 95-1 (version ———— and 95-2 signed the consent form on the same day as the MTT procedure.

Your response dated October 2, 2001, describes that the informed consent process began during screening and was formally completed with the act of signing the consent form on the day of the MTT procedure.

The protocol requires that the informed consent process be completed ———— in advance of MTT, *before* the study-related procedures are initiated. You repeatedly violated these protocol requirements during the period from 1993 until 1999.

3. **You failed to ensure that the informed consent was obtained and documented in accordance with 21 CFR Part 50. [21 CFR § 312.60].**

A. The protocols require cyclosporine dosing in advance of the MTT procedure. Study records reveal that prospective subjects were instructed to initiate dosing with cyclosporine before the consent form was signed and before they were informed of the risks associated with cyclosporine. As noted in item 2K above, at least— subjects (under protocols 93-5, 95-1, and 95-2) signed the consent form on the same day as the MTT procedure and *after* cyclosporine dosing. In other words, they participated in the study without being advised of the reasonably foreseeable risks or discomforts in violation of 21 CFR 50.25. The information in the "Parent's Pak" did not address the risks of cyclosporine and records indicate parents did not know of the serious adverse events that could occur. The consent forms for studies 93-5, 95-1, and 95-2 state the following:

> Prolonged use of cyclosporine at high doses can cause kidney/liver intoxication, abnormally high blood pressure, carcinoma, and convulsions...Other common reactions include excessive hair growth, tremor, blood clotting, abnormal gum growth, and tingling. Patients taking cyclosporine have a slightly increased risk of infection.

You failed to address this violation in your response letters. Cyclosporine issues are also discussed in item 5B below.

B. Subjects' representatives signed the consent form on the day of the transplant procedure. You performed extensive screening evaluations and required the prospective subjects to travel, often at great distance and

expense, to your location before the consent interview was completed. The manner in which you obtained the informed consent from subjects' representatives did not provide the representative sufficient opportunity to consider whether to participate and did not minimize the possibility of coercion or undue influence. By the time you sought written consent, the subjects' family had significant financial expenses and emotional investment in the prospect of participating in the study. Reading the information you supplied to the subjects' family in the "Parents' Pak" does not fulfill the requirement of informed consent.

Your response dated October 2, 2001, explains that the consent process began when subjects and their families first visited the sponsor facility to be evaluated to determine whether they were eligible for the study. You state that you explained the investigational nature of the study, the potential risks and benefits, and provided the "Parents' Pak" to those subjects determined to be eligible. Yet, you failed to complete the informed consent process by obtaining the written informed consent from the subjects' representatives at this time. See also item 2K above. Although you may have initiated the consent process during the screening visit, you did not complete the informed consent process until immediately prior to the MTT procedure. Obtaining consent at this juncture, *after* the subject had already begun participation in the study by cyclosporine dosing, after a second international and/or long-distance journey to Memphis, TN, and after the subject and his representatives had paid the sponsor as much as $150,000, did not minimize the possibility of coercion and undue influence as specifically required by the regulations.

C. You failed to provide the subjects or their representatives a consent form in the language understandable to them. Your records indicate that many subjects from foreign countries were not provided with informed consent documents and the "Parent's Pak" written in the subject's or the representative's own language. The regulations require that any information given to the subject or the representative shall be in language understandable to them.

Additionally, you failed to provide instructions for cyclosporine dosing and the required follow-up lab testing to maintain safe dosing in a language understandable to the subjects or their representatives because you provided all subjects or their representatives with dosing instructions written in English. The medical staff who performed the investigational procedure communicated with the subjects and the subjects' representatives through a translator.

Protocol	Subjects	Homeland
93-5	[redacted]	[redacted]
93-5	[redacted]	[redacted]
93-5	[redacted]	[redacted]
93-5	[redacted]	[redacted]
93-5	[redacted]	[redacted]
93-5	[redacted]	[redacted]
95-1	[redacted]	[redacted]
95-1	[redacted]	[redacted]
95-1	[redacted]	[redacted]
95-1	[redacted]	["interpreter" - native language unknown]
95-1	[redacted]	[Spanish-speaking]
95-2	[redacted]	[redacted]
95-2	[redacted]	[Spanish-speaking]
95-2	[redacted]	[redacted]

Your response letter dated October 2, 2001, explains that interpreters accompanied non-English-speaking subjects and their representatives to the sponsor facility and that it was common for the interpreter to read the consent form "line by line" to them prior to the MTT procedure.

Your explanation does not address a serious violation of the general requirements of informed consent that affected the safety of your studies' design: that as a part of the study, the subjects' families were responsible for administering cyclosporine -- a dangerous immunosuppressive agent that can cause severe toxicity -- and you provided written instructions in a language that was not understandable to the subjects' representatives. Although you claim that interpreters "were present when necessary" while the subject was at the sponsor's facility, the subjects were required to adhere to the cyclosporine regimen while at home. There is no documentation that the subjects' representatives had access to interpreters to translate the study requirements including the instructions for cyclosporine dosing and testing at home. Additionally, 21 CFR 50.27 requires that you provide the person signing the consent form a copy of what is signed. This requirement allows the subject or representative

adequate opportunity to read the form. Because you provided only an English version, you denied many subjects and their representatives this opportunity to read and consider what was involved with the study.

4. **You provided incomplete or inaccurate information to the IRB, which the IRB used as the basis for its initial and continuing review and approval decisions. [21 CFR § 312.66].**

A. With the exception of two subjects from——— approved by the IRB in 1999, you failed to inform the IRBs that you enrolled a significant number of non-English speaking subjects from foreign countries. Without this important information, the IRB did not have the opportunity to deliberate on additional consent procedures to protect the rights of these subjects.

Your letter dated October 2, 2001, states that you did not withhold this information because you were not required to notify the IRB that you were recruiting non-English-speaking subjects from foreign countries.

On the contrary, the language barrier may contribute to the situation in which some subjects are vulnerable to coercion or undue influence, especially because the subjects have acute and/or severe physical illness. Furthermore, in your explanation of item 2A above, you acknowledge that some subjects from other countries did not have access to health care facilities that were adequate to perform the cyclosporine level testing required by the study. In the context of the demanding study requirements for testing and monitoring while at home, the IRB needed to be advised that subjects were from foreign countries in order to consider the subjects' access to health care facilities and accordingly, the subjects' ability to participate in the studies.

B. You failed to submit the "Parents' Pak" information package for IRB review.

Your response letter dated October 2, 2001, describes the "Parents' Pak" as an informational package of materials "to help subjects and their families understand the nature of the Myoblast Transfer Therapy (MTT) process" that does not require IRB review and approval.

We do not accept your explanation. Your letter dated October 2, 2001, explains that the "Parents' Pak" provided information that was not intended to influence whether prospective subjects chose to consider participation in the research. The "Parents' Pak" contains specific information about the required procedures before, during, and after the investigational procedure in more detail than the informed consent document. The "Parents' Pak" required IRB review because it is the only document that provides detailed information about the testing and

procedures that are required before the investigational procedure may occur, and, as such, is integral to the informed consent process.

C. The status report you submitted to the Baptist Memorial Hospital Patient Participation Committee on———— did not provide accurate information as to the reason why subjects withdrew or dropped out from study 95-2. You reported that four subjects dropped out due to "difficulties in travel every 3 months." However, records obtained by FDA during the inspection revealed that one subject dropped out because the subject's parents did not see any significant improvements after six months post "myoblast transfer therapy."

Your response letter dated September 2, 2000, acknowledges this violation.

5. **Failure to maintain adequate and accurate case histories designed to record all data observations pertinent to the investigation. [21 CFR § 312.62(b)].**

A. The case report forms for subjects and donors do not accurately record the occurrence of adverse events that are documented in the medical records. The following table presents examples of adverse events omitted from the case report forms; this is not a complete list:

Subject	Protocol	Adverse Event Documented in Medical Records	Adverse Event As Documented on Case Report Form
	93-5	Nausea, vomiting, pain (MTT# — and MTT —	Nausea="No" Vomiting="No" Pain="No"
	93-5	Nausea, vomiting, upper body pain, bruises	Nausea= " - " Vomiting= " - " Pain= " - " Ecchymosis= " - "
	95-1	Nausea, vomiting	Nausea="No" Vomiting="no"
	95-1	Nausea, vomiting, pain requiring Demerol and Tylenol 3, continuing at discharge.	Nausea="No" Vomiting="No" Pain="Minimal"
	95-2	Pain	Pain="No"
	95-2	Nausea, vomiting, fever	Nausea="No" Fever="No" Vomiting="no"

Your response letter dated October 2, 2001, explains that these examples are "clerical errors" and are "relatively minor." On the contrary, the accurate recording of nausea and vomiting events are especially important because the informed consent documents for studies 93-5, 95-1, and 95-2 do not identify these conditions as possible discomforts that might occur as a result of the investigational procedure.

B. You did not maintain disposition records to account for the quantities of cyclosporine provided to each study subject as part of the investigational plan. There are no records of the following: (1) initial cyclosporine dosage calculations for each subject, (2) who wrote the prescription order, (3) when the prescription was written, and (4) how much cyclosporine was dispensed to each study subject.

Your response letter dated October 2, 2001, claims that cyclosporine was not the study drug, and, therefore, there was no requirement for such information to be documented.

On the contrary, complete and accurate records on the use of cyclosporine in conjunction with the investigational drug are required to determine the safety and efficacy data of your clinical studies. Your response misrepresents the true meaning of 21 CFR 312.62(b). Contrary to your claim, the issue is not simply the lack of regulatory requirement for maintaining disposition records for an approved drug. The important issue is your failure to maintain adequate and accurate records pertinent to the clinical study and the safety of study subjects.

Inappropriate cyclosporine dosing can lead to serious side effects, including renal and hepatic toxicity. The two boxed warnings on the approved labeling for cyclosporine clearly highlight the fact that only physicians experienced in immusuppressive therapy and management of organ transplant patients should prescribe this drug. Furthermore, patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. Careful monitoring of cyclosporine serum levels, drug dosing adjustments, and patient follow-up are critical to ensure subject safety.

C. Protocol 95-1 requires that donors must have a negative rapid plasma reagin test (RPR). Donor —— for Subject # — did not have RPR results in his file. Your written response dated September 6, 2000, acknowledges this violation.

Your written request for a hearing must be postmarked, if mailed, or received, if faxed (with the original to follow by mail), within ten (10) working days of receipt of this letter. Please address the letter to:

Dr. James F. McCormack, Coordinator
Bioresearch Monitoring Program
Division of Compliance Policy (HFC-230)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
Telephone (301) 827-0425
Facsimile (301) 827-0482

If no response to this letter is received by that time, you will be deemed to have waived your right to a regulatory hearing, and a decision in this matter will be made based on the facts available to the agency.

A request for a hearing may not rest upon mere allegations or denials but must present specific facts showing that there is a genuine and substantial issue of fact that warrants a hearing. Pursuant to 21 CFR §16.26, a request for a hearing may be denied, in whole or in part, if the Commissioner or his delegate determines that no genuine and substantial issue of fact has been raised by the material submitted. A hearing will not be granted on issues of policy or law. Written notice of a determination of summary judgment will be provided, explaining the reasons for denial of the hearing.

If you wish to respond but do not desire a hearing, you should contact Dr. McCormack within the time period specified above and send a written response containing your reply. The letter should state that you waive your right to a hearing and that you want a decision on the matter to be based on your written response and other information available to the agency.

The agency's offer to enter into a consent agreement remains open. Entering into a consent agreement would terminate the administrative procedures, but would not preclude the possibility of a corollary judicial proceeding. You were sent a draft consent agreement enclosed with FDA's letter dated August 17, 2001. If you would like to choose this option, please contact Dr. McCormack.

No final decision by FDA has been made at this time on your eligibility to continue to use investigational drugs. Moreover, there will be no prejudgment of this matter if you decline to enter into a consent agreement and decide instead either to request a regulatory hearing or to request that the decision be based on information currently available to the agency.

Please inform Dr. McCormack within ten (10) working days whether you wish to request a hearing or to have this matter resolved by consent agreement or based on the information available to the agency.

Sincerely yours,

John M. Taylor
Senior Associate Commissioner for
Regulatory Affairs

Enclosures
21 CFR Part 10, Subpart C
21 CFR Part 16
21 CFR Part 312