

Congress of the United States
House of Representatives
Washington, DC 20515-0529

HENRY A. WAXMAN
29TH DISTRICT, CALIFORNIA
February 23, 2000

Dr. Ruth Kirschstein
Acting Director
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20892

Dear Dr. Kirschstein:

I am writing to let you know of my deep concern about the adverse event data from gene therapy trials overseen by the National Institutes of Health (NIH). This new information shows an inexplicable noncompliance with NIH gene therapy guidelines and suggests that NIH's oversight has been inadequate.

As you know, I first wrote requesting information about adverse event reports in November 1999. Since then, I have been surprised and disappointed by the NIH's lack of cooperation in sharing information and supplying constructive analysis. In fact, it has been extraordinarily difficult and time-consuming simply to receive a complete accounting of both the adenoviral and non-adenoviral gene therapy trial protocols.

Despite these obstacles, my staff—with the assistance of the minority staff of the House Commerce Committee—has conducted a preliminary review of the NIH's gene therapy adverse event reports. In addition to documenting numerous late adverse event reports in non-adenoviral trials, our analysis indicates that for years many of the investigators and sponsors provided no information of any kind to the NIH concerning the deaths, life-threatening events, and injuries taking place in their research. Moreover, the reports received by the NIH in response to its October 1 and November 22, 1999, appeals for adverse event data were frequently incomplete or undated.

The most recent reports raise new questions about the conduct of gene therapy trials, the lapses in compliance, and the adequacy of federal oversight. Three trials, in particular, illustrate the apparent seriousness of these problems:

- In one trial, a 1996 patient death was reported and lab tests were promised to assure no causal relation to the gene therapy. But no results were apparently provided by the investigator or sought by the NIH, even after your agency's 1999 appeals for information.
- One trial—of the many that continually provided no reports to the NIH—stands out because 38 of its 48 patients “die[d] between study initiation and completion” and it had “1,112 [adverse] events of which 281 were considered related to treatment.”

NIH Acting Director Ruth Kirschstein, M.D.

February 23, 2000

Page 2

- In a third trial, an NIH pharmacy shipped the wrong medication, which was actually administered to patients in a gene therapy trial. Yet no information was provided on how the NIH's error was discovered or the agency's plans to prevent such potentially life-threatening failures in the future.

Given my recent experiences with your agency, I am skeptical that additional information can help explain why the NIH didn't adequately investigate the 1996 death of one patient, why it shipped the wrong medication to some patients, or why it didn't take any action in a trial that resulted in the deaths of three out of every four patients participating in it. Nonetheless, it is important for Congress to try to have as much information as possible, so I would appreciate receiving your response to the following questions and any mitigating facts that you believe may provide a context for these intolerable incidents.

A. Trial 9212-035 – “Gene Therapy of Cystic Fibrosis Using E1 Deleted Adenovirus: A Phase I Study” – James M. Wilson, University of Pennsylvania Medical Center; Richard H. Simon, University of Michigan Medical Center; Karen McCoy, Ohio State University

On March 11, 1996, University of Pennsylvania researchers wrote a brief three-paragraph letter to NIH Office of Recombinant DNA Activities (ORDA) Director Nelson Wivel “to report the death of one of our patients.” The letter states: “Lung tissue has been harvested and the Institute is currently running tests for expression of gene transfer and adenovirus persistence. We will forward these results to you as soon as they are available.”¹

One of the NIH's most fundamental responsibilities is to ensure that an experimental treatment doesn't cause the death of patients. I don't see any information in the record, however, that indicates any scrutiny of a possible causal relationship between the trial's treatment and the patient's death. If so, this would be an egregious failure by the NIH.

To help clarify these issues, please respond to the following questions:

- Did the NIH receive the test results in 1996? If not, were they included in the Penn Institute for Human Gene Therapy's October 20, 1999 submission of summary data for all of its gene therapy trials?
- If the test results still have not been submitted by the Penn Institute, do you agree that this represents a glaring oversight in the exercise of the NIH's responsibilities? What steps has the NIH taken to obtain the results? And is the NIH now actively investigating a causal relationship between the gene therapy and the patient's death?
- What impact did the unprecedented hiatus in the Recombinant DNA Advisory Committee's (RAC) oversight following NIH Director Varmus' 1996 decision to abolish it have on the lack of documented follow-up by the NIH in 1996? What impact did the turnover in NIH Office of Recombinant DNA Activities (ORDA) personnel have on NIH follow-up?

¹ Letter from Dr. James M. Wilson and Dr. Cynthia Robinson to Dr. Nelson A. Wivel (March 1996).

B. Trial 9406-079 – “A Tolerance and Efficacy Study of Increasing Doses of Adenoviral Vector Expressing Wildtype p53 Administered with Cisplatin in Patients with Non-Small Cell Lung Cancer” – Jack A. Roth and John Nemunaitis, M.D. Anderson Cancer Center

In its October 22, 1999 summary report to the NIH, Introgen Therapeutics disclosed that, of the total 48 patients in this trial, 38 “died between study initiation and completion,” “35 serious adverse events were experienced by 28 patients” and “there were 1112 total [other] events of which 281 were considered related to treatment.”²

It would seem obvious that there would be vigorous and immediate oversight of any protocol that results in the deaths of 75% of the participating patients. There is no indication, however, that the NIH has taken any action in this matter. Does the NIH believe that the severity of the disease being investigated explains the trial’s high mortality and justifies the apparent lack of follow-up activity by the agency? In addition, please respond to the following:

- When did the NIH first learn of these 38 deaths?
- Did the NIH consider the large number of deaths unusual and of concern? What has the NIH done to investigate this matter?
- The information on the 35 serious adverse events, as well as the patient deaths “possibly related” to the therapy, is brief and provided only in summary form. Does the NIH consider this information adequate to confirm whether the sponsor’s judgments regarding causation are accurate?
- The summary of adverse events was apparently provided to the NIH three years after they occurred by the corporate sponsor of this trial. Was there an earlier indication of problems by the investigators of the study? If not, and investigators violated the NIH Guidelines, did the corporate sponsor have a responsibility to inform you in a more timely manner? If you do not view the corporate sponsor as responsible, what steps need to be taken to ensure responsibility in such instances?

C. Trial 9706-193 – “A Phase 1 / 2 Study of Sequential Vaccinations with Vaccinia CEA and ALVAC CEA with the Addition of IL-2 and GM CSF in Patients with CEA Expressing Tumors” – James L. Marshall, Georgetown University Medical Center

On December 8, 1999, a National Cancer Institute (NCI) pharmacy shipped the wrong medication to Georgetown University Hospital, where it was administered to six patients in a gene therapy trial. On December 27, Dr. James Marshall informed the FDA that “[s]ix patients who were enrolled” in the NIH-sponsored gene therapy trial “were administered ALVAC IL-12 instead of ALVAC CEA.”³

² Introgen Therapeutics, *Adenoviral Vector Safety and Toxicity Reporting Form* (October 21, 1999).

^{3,4} Letter to FDA CBER Director of Vaccines Research and Review Karen Goldenthal from Dr. John L. Marshall (December 27, 1999).

NIH Acting Director Ruth Kirschstein, M.D.

February 23, 2000

Page 4

Providing the wrong medication to patients is an act of inexcusable incompetence. The fundamental question is whether this was an isolated instance or whether other similar mistakes are possible. To address this issue, please respond to the following:

- What is your explanation for the mistake made by the NIH? Was there a second mistake by Georgetown University in failing to recognize the problem?
- The NIH data do not disclose how the NCI discovered the error or whether the NCI computer failure resulted in other dispensing and shipping errors for other protocols or patients. Nor do the data include the agency's plans to prevent such potentially life-threatening failures in the future. Please provide this information.
- Georgetown University Hospital convened an internal review committee to implement steps to prevent such medication errors in the future. Dr. Marshall reported, "The findings [of] that committee will be forwarded once the special report has been completed in January 2000."⁴ As of February 9, however, your agency had apparently either failed to receive the report or did not make it available. Please explain this and provide a copy of the report.
- Are you aware of other trials that resulted in mistakes in administering medication?

The sheer volume and variety of noncompliance with the NIH Guidelines evident in the gene therapy serious adverse event data is extremely troubling in itself. It also underscores, however, the absolute need not only for federal regulation, but for federal regulation that is competent and comprehensive.

Thank you for your assistance, and please ensure that I receive your response by March 1.

Sincerely,



HENRY A. WAXMAN
Member of Congress

cc: The Honorable Donna Shalala
Secretary of Health and Human Services