BURZYNSKI
RESEARCH INSTITUTE, INC.

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Michael A. Friedman, M.D.
Associate Director
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Division of Cancer Treatment, NCI
National Institutes of Health
Executive Plaza North, Room 742
Bethesda, MD 20892

Dear Dr. Friedman,

In response to your letter of October 20, 1993, it is difficult for me to understand why the entire first page of your letter is used to discuss the simplest issue: that adults should use a different dosage than that for children. Since you agreed to the study procedure of Protocol BT-6 as recommended in my letter of June 9, 1993, we have not requested any changes in the structure of treatment which was accepted by Memorial Sloan-Kettering Cancer Center (MSKCC). As you confirmed in your letter of October 20, 1993, you know very well that since April of this year my recommended dosage of Antineoplaston AS2-1 for adults is 0.4g/kg/24h. Again, I confirmed that this is the right dosage for adults in my letter to Dr. Shoemaker of August 24, 1993. Yet, for no apparent reason, you insist on using in the adult treatment protocol the dosage 0.6g/kg/24h which I recommend for children.

It is generally known that a child's body weight is much lower than that of adults. This should be reflected in the escalation of the dosages. My recommendation as to how to escalate the dosages for adults was submitted to the NCI on June 4, 1992. Yet, for no apparent reason the MSKCC protocol, which is designed for adults, escalates the dosages in the small increments recommended for children. The principle behind dosage escalation is to accomplish the maximum dosage in three to five days, not three to four weeks, which would expose the patient to the unnecessary risk of tumor progression.

I appreciate very much that you have finally decided to follow my recommendation regarding dosage and dosage escalation.

Regarding the number of patients to be treated at MSKCC, the contradictory, incomplete, and inconsistent information is being supplied by you. The MSKCC's protocols of April 16, July 13, and August 30, 1993 describe the treatment of 35;

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but not 70 patients (please see paragraph 12.1, page 10 of the protocol, which is attached). It was our understanding that 35 patients would be treated at MSKCC and at the Mayo Clinic. I never agreed for the treatment of 70 patients at MSKCC. Since I have to produce the medicine for the trial and pay for it, it is vitally important to me to know how many patients will be treated. The treatment of an additional 35 patients may cost us up to two million dollars. Contrary to the information given by NCI that we received the money for the production of medicine, this money went apparently into a "black hole" ("Black Holism," The Village Voice, July 29, 1993, enclosed). We have received none of the money which the Office of Alternative Medicine gave to the NCI for funding the trials with our medicine.

Contrary to the opinion expressed in your letter, we see no reason for modifying Fleming's Phase II clinical trial design and introducing more stringent than usual criteria for response evaluation. We request that Fleming's original design be used, which calls for the initial treatment of 15 patients with at least one responder, instead of 20 patients and two responders. Given the fact that there is no existing treatment effective in this type of cancer, one responder in 15 is certainly significant and would be reason enough to expand the trial.

I found your requirement for 14 days to complete scans and laboratory tests prior to treatment very interesting. It is a very well known fact that glioblastoma multiforme is such an active tumor that if two weeks elapses from the time of the scan and the beginning of treatment, the tumor may increase by more than 50%. This means that even before the patient begins treatment, he can be classified as an increasing disease case. In most of the hospitals in the U.S., including our tiny clinic, all pretreatment tests including scans can be done in one day. Therefore, I insist that the pretreatment evaluation, including brain scans, be done within seven days from the time treatment begins.

Regarding the Karnofsky Performance Status (PS), it is unclear to me why you have backed off from your own recommendation in your letter of May 5, 1993 (copy attached) that "patients with Karnofsky PS of below 70% should be excluded." I am requesting that as recommended by NCI, the patient's PS should be 70% to 100%.

I agree that both scan data and neurological assessment can be described in the analysis of response, but the decision of how to classify response should be based on tumor measurements alone. All of these patients will have been extensively treated before. As the result of previous neuro-toxic treatments, a number of these patients will deteriorate neurologically even if the Antineoplastons eradicate the

tumor. The purpose of the protocol is to evaluate the antitumor effect, not to prove that Antineoplastons can repair brain damage resulting from chemotherapy and radiation.

In this first independent study with Antineoplastons, in order to assure that patients will derive the most benefit from the treatment, it is critically important to schedule more frequent evaluations of the data than waiting until after the accrual of 14 patients, i.e. waiting nine months. (Based on an accrual of 2 patients per month, if we wait until 14 patients are accrued and treated, nine months will pass before the first evaluation takes place). Therefore, I request that reviews of the studies be performed after the treatment of each group of five patients, i.e. after six months. I agree, however, that you will provide the Theradex printout to us as you receive it.

In addition to patient welfare, there is another reason for more frequent evaluations. As you stated in your letter, I have no doubt that the investigators at MSKCC have extensive experience treating glioma. However, MSKCC is known to be biased against Antineoplastons. At least three researchers associated with MSKCC published willful misrepresentations and distortions about Antineoplaston research. Because of the controversial nature of the upcoming Antineoplaston clinical trials, it is essential that they are conducted in a manner beyond any suspicion of bias.

Contrary to the opinion expressed in your letter, NCI is responsible for the trial's delay. As you well know, the NCI selected an MSKCC investigator in September, 1992. In spite of our repeated requests, eight months were wasted before the NCI produced the first draft of the protocol. As promised in my letter to you of November 5, 1992, the supply of Antineoplastons has been prepared and was shown to Ms. Mary McCabe of NCI during the site visit on February 9, 1993. The medicine was ready to be released pending final approval of the labels by the FDA and our final QC inspection. The medicine will be sent to you immediately once you make the corrections to the protocol that we have requested.

Since you mentioned that patient recruitment has begun already, I would be glad to accept these patients immediately under my care and offer them free medicine as we wait for the protocol to be revised and the treatment at MSKCC to begin. The MSKCC protocol in its current form would threaten the welfare of these patients.

In your letter you stated that your mission is to find and develop better therapies for cancer patients, and that your only obligation is to those patients. However, the way

you proceed leads me to question that for the following reasons:

1) Out of numerous cancer treatment centers, you selected two: MSKCC and Mayo Clinic, which are known to be strongly biased against alternative treatments. In the past doctors associated with MSKCC have voiced strong opposition to Antineoplaston therapy and have published articles full of misrepresentations and distortions.

2) The protocol approved by you will allow the disease to progress between the pretreatment evaluation and the beginning of treatment.

3) Due to the slow escalation of dosages, patients will most likely have a marked increase of tumor size before beginning the treatment at the correct dosage level.

4) In spite of my numerous requests (letters of April 29, June 9, and August 24, 1993) to proceed following the guidelines of the NCI's Decision Network on December 2, 1991 to have a separate clinical trial for glioblastoma multiforme and anaplastic astrocytoma, you continue to combine both types of tumors together. Even in your most recent stratification strategy submitted to the FDA, you are planning to treat initially 20 patients without specifying whether these 20 patients are per each stratum (glioblastoma vs. anaplastic astrocytoma), or whether this initial group of 20 patients consists of a mixture of glioblastoma and anaplastic astrocytoma. If the latter is the case, then we can expect that among these first 20 patients, most will have glioblastoma, which is more common and more difficult to treat. In case of treatment failure in these first 20 patients, it will be easy to make the statement that Antineoplastons do not have therapeutic effect in both tumor categories.

5) The protocol now states in paragraphs 10.2, 10.3, and 10.4 that the objective decrease of tumor size is not enough to be considered a true response to treatment, that there must also be improvement in neurological function. As I explained in my letter of October 13, 1993 to Dr. Greenblatt, it is not unusual in my practice to see patients whose tumor has disappeared, but who have deteriorated neurologically as the result of delayed toxicity from radiation therapy and chemotherapy. Since these patients in the MSKCC study have been pretreated, and since there has been no indication that anything, including Antineoplastons, can repair brain damage caused by chemotherapy and radiation, I request that the criteria including restored neurological functioning be removed from paragraphs 10.2, 10.3, and 10.4 of the protocol.

6) Finally, by limiting our access to the data and not allowing review until after the first 14 patients have been treated, it would be easy to deviate from the protocol and supply inadequate treatment, and then claim that due to the failure of the first 14 patients it would be a waste of the taxpayers money to proceed with further treatment.

Your final statements that you are ready to proceed with the treatment with Antineoplastons without our participation caught me by surprise. It is hard to imagine that a Federal employee would consider patent infringement, thus infringing on the patent rights of thousands of our shareholders.

Once again, I urge you to take our requests seriously, honor the guidelines of the NCI's Decision Network on December 2, 1991, and make proper corrections to the protocol, so that objective clinical studies can begin immediately. In the meantime, I would be glad to treat for free all the patients presently recruited, and will submit progress reports weekly for the NCI's review and evaluation.

Sincerely,

S. R. Burzynski, M.D., Ph.D.

SRB/cf

cc: Senator Joseph Biden
Senator Barbara Boxer
Senator Dianne Feinstein
Senator Tom Harkin
Senator Barbara Mikulski
Congressman Berkley Bedell
Congresswoman Nancy Pelosi
Dr. Samuel Broder
Dr. Jan Buckner
Dr. Bruce Chabner
Dr. Daniel Eskinazi
Dr. Jay Greenblatt
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Ms. Dorothy Tisevich