BURZYNSKI RESEARCH INSTITUTE, INC.

October 4, 1988

Dvorit Samid, Ph.D.
13 Tapiola Court
Rockville, MD 20850

Dear Dr. Samid,

Bob DeBragga requested that I send the enclosed information to you concerning the work of Stanislaw R. Burzynski, M.D., Ph.D.

In brief, Dr. Burzynski began his work 21 years ago with a group of peptide growth inhibitors which he identified and named "antineoplastons" due to their activity in inhibiting neoplastic cell growth. According to his research, these peptides are produced by a biochemical defense system which is completely different from our immune system. The fact that antineoplastons literally reprogram cancer cells makes this a most attractive possibility for cancer treatment.

Equally of note is his discovery that these peptides are effective in not only treating cancer, but in diagnosing and preventing it as well. The Medical College of Georgia, the University of Kurume Medical School in Japan, and the Burzynski Research Institute in Houston have recently completed animal studies that indicate that low doses of synthetic Antineoplaston A10 taken orally can prevent lung, breast, and liver cancers in animals.

Antineoplaston treatment is a self-administered, out-patient cancer chemotherapy treatment which is normally free from the usual side effects of conventional chemotherapy. The majority of Dr. Burzynski's patients since 1977 have responded positively to antineoplaston treatment.

If you would like additional information, we would be delighted to bring you to Houston as our guest to meet with Dr. Burzynski and tour our clinic, research laboratory, and pharmaceutical production facility. Dr. Burzynski would love to meet with you and share his research.

Our best wishes,

Le Trombetta
Director of Public Information

Enclosures

cc: Bob DeBragga

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UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
F. EDWARD HÉBERT SCHOOL OF MEDICINE
4301 JONES BRIDGE ROAD
BETHESDA, MARYLAND 20814-4799

PATHOLOGY

October 12, 1988

TEACHING HOSPITALS
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NAVAL HOSPITAL, BETHESDA
MALCOLM GROW AIR FORCE MEDICAL CENTER
WILFORD HALL AIR FORCE MEDICAL CENTER

(301)295-3480

Stanislaw R. Burzynski, M.D., PH.D.
The Burzynski Research Institute
6221 Corporate Dr
Houston, Texas 77036

Dear Dr. Burzynski;

I was most excited to hear about your work and would be very pleased to collaborate in research on the antitumor action of Antineoplastons.

We are currently engaged in studies on tumor suppression by biologicals, using oncogene-transformed and spontaneous tumors as model systems. The A2 appears very attractive because we are looking for agents that could reprogram tumor cell behavior (induce phenotypic reversion or terminal differentiation). A2, and possibly also A10, could be included in our studies. If you agree, please provide me with the substances and related information. Specifically, I need to know whether you have anti-A2 antibodies and/or knowledge of the peptide sequences. Since you have mentioned the problem of obtaining sufficient amounts of A2, I have thought of the potential for DNA cloning of A2 active peptides, but this should be considered only after we perform preliminary investigations.

I would appreciate your opinion regarding the choice of peptides and the appropriate experimental design. Some of the experimental approaches applied routinely in our laboratory are:

I. <u>In vitro</u> experiments.

1. Treated tumor cells are examined at different time points for biological changes, including reduced cell proliferation, cell death, terminal differentiation and phenotypic reversion.

2. Molecular analysis of gene expression. Alterations in expression of oncogenes and other transformation-related genes are being evaluated using specific radiolabeled DNA/RNA probes (and some immunochemistry or functional assays).

3. DNA-mediated oncogene transfer experiments. These are applied to test the ability of agents to prevent neoplastic transformation.

II. In vivo studies in athymic nude mice.

1. Inhibition of tumor growth.

2. Prevention of tumor metastasis.

We have several models of human malignancies (including breast carcinomas, melanoma and osteosarcoma) all of which can grow not only as primary tumors, but also form lung metastases in the immunodeficient mouse. As you know, such human models are rare. I believe that these (and not animal tumor models) should be applied in testing therapeutical agents.

Please let me hear from you soon.

Sincerely yours,

D. Samid

Dvorit Samid, PhD
Assistant Professor

enc.

BURZYNSKI
RESEARCH INSTITUTE, INC.

November 7, 1988

Dvorit Samid, Ph.D.
Assistant Professor
Uniformed Services University
of the Health Sciences
Department of Defense
4301 Jones Bridge Road
Bethesda, Maryland 20814-4799

Dear Dr. Samid:

I read with great interest your letter of October 12, 1988. Your proposed in vitro and in vivo experimental approaches are very exciting. I agree that Antineoplaston A2 seems to be the most attractive agent to be tested in vitro, especially in experiments where treated neoplastic cells are examined at different time intervals for terminal differentiation and phenotypic reversion. Molecular analysis of gene expression also looks very promising. I believe it will be a good idea to consider experiments with Antineoplaston A10 to test its ability to prevent neoplastic transformation.

I think it will be also attractive to test Antineoplaston AI0 and Antineoplaston A2 in breast carcinoma and malignant melanoma. As I mentioned to you, we have currently problems in obtaining large amounts of Antineoplaston A2 but we have sufficient quantities of Antineoplaston A10. We will do our best to prepare a sample of Antineoplaston A2 for you as soon as possible. Unfortunately, we do not have anti-A2 antibodies, and we are currently involved in purification and peptide sequencing. It looks like DNA cloning of A2 active peptides will be a method in the future.

Attached to this letter, you will find the newest edition of our publications which I received last month, and which will give you details on some of the experiments we did regarding differentiation inducing potential of Antineoplastons. Shortly, we will send you a sample of Antineoplaston A2.

We appreciate very much your interest in our work.

With kind regards,

Sincerely yours,

S. R. BURZYNSKI, M.D., Ph.D.

SRB:ss
Encl.

6221 CORPORATE DRIVE • HOUSTON, TEXAS 77036 • (713) 777-8233

BURZYNSKI
RESEARCH INSTITUTE, INC.

January 9, 1989

Dvorit Samid, Ph.D.
Assistant Professor
Uniformed Services University
of the Health Sciences
Department of Defense
4301 Jones Bridge Road
Bethesda, Maryland 20814-4799

Dear Dr. Samid:

As we discussed in our previous correspondence, I am providing you a sample of 1.009 grams of Antineoplaston A2 for your experiments (Lot No. 283XP.) Due to the Federal regulations, I have to inform you that the sample is not for human use but for animal experimental use only.

Please let me know about your test results.

With kind regards,

Sincerely yours,

S. R. BURZYNSKI, M.D., Ph.D.

SRB:ss

Encl.

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PATHOLOGY

TEACHING HOSPITALS
WALTER REED ARMY MEDICAL CENTER
NAVAL HOSPITAL, BETHESDA
MALCOLM GROW AIR FORCE MEDICAL CENTER
WILFORD HALL AIR FORCE MEDICAL CENTER

September 19, 1989

Stanislaw R. Burzynski, M.D., PH.D.
The Burzynski Research Institute
6221 Corporate Dr
Houston, Texas 77036

Dear Dr. Burzynski;

I was good taking with you last week. As we discussed, I would like to initiate studies in my laboratory on the anticancer activities of A2. While I may be able to carry some preliminary experiments with my current budget, it would be critical that additional funding will become available soon. Some of the experiments to be considered are:

A. Investigations of the Anti-Tumor Effects of A2. In the first phase, I plan to examine the effect of A2 on a panel of human tumor cell lines with known activated oncogenes. This will allow for a simultaneous cellular and molecular analysis focusing on:

(1) Alterations in growth characteristics (e.g., arrest of cell proliferation, phenotypic reversion, and differentiation).
(2) Modulation of expression of oncogenes and other transformation-related genes. The molecular analysis would employ nucleic acid probe technology, immunochemistry, and some functional assays.

The in-vitro studies will be extended to patients' tumor samples. We have a system in which solid tumor biopsies can be kept in a 3D organ culture, a condition allowing to study growth arrest and differentiation, and to perform in-situ analysis of gene expression. This system could be used to evaluate the response of specific tumor types to single-, and combination treatment protocols. In a few instances, the in-vitro studies will be complemented with in-vivo studies using an animal model of athymic mice bearing primary or metastatic human tumors.

B. Molecular Cloning of DNA Sequences Coding for A2 Peptides. For these studies we will need to obtain either anti-A2 antibodies or information on peptide sequences. The antibodies, or synthetic oligonucleotides generated based on predicted DNA codons, will be used as probes to screen an expression cDNA library made from normal human embryo fibroblasts. [The assumption here is that these cells produce A2-related peptides. [... Please let me know if you have information regarding A2 production by different tissues]. It may be important also to clone the gene(s) from tumor cells in order to identify the changes underlying the malfunction of A2 peptides in cancer patients.

The cloned gene(s) could then be used to address questions such as:

(1) Is there a correlative between A2-related gene expression and neoplasia ? This will be evaluated by screening cell lines as well as patients' tumor biopsies using the cloned sequences as a probe.
(2) What mechanisms block A2 activity ? In case of quantitative differences in gene expression in normal vs cancer cells, we will use the cloned DNA from normal cells to pull the corresponding sequences from a genomic DNA library prepared from cancer cells, and then search for problems related to regulation in gene expression. Alternatively, if there will appear to be a qualitative difference, cDNA clones will be obtained from tumor cells and the DNA sequences compared to those of the normal allele.
(3) Would restoration of A2 activity cause phenotypic reversion ? The gene(s) clones from normal human cells, put into appropriate expression vectors, can be used in re-constitution studies (gene transfer to cancer cells) to evaluate their potential to restore normal growth characteristics. These could also be used to obtain large amounts of biologically active products in bacterial or mammalian systems.

As you see, the investigations could develop in so many interesting directions, and be most rewarding in terms of better understanding the mechanisms of action of the antineoplastons. The program is obviously very challenging and laborious. However, your exciting clinical experience with A2 and A10 no doubt justify such a research effort. I will initiate the molecular studies once the anticancer activities of A2 are demonstrated in my laboratory and the appropriate model systems for DNA cloning work identified. I have the know-how, a group of enthusiastic and talented investigators, and a laboratory equipped with the major tools needed for the biological and molecular studies. The pace at which the program could develop depends, among others, on the budget. We could start with a modest budgets: as little as $50K/year in direct cost would support one research assistant and cover other expenses (supplies, animals, administrative help, etc). As you must know from your own experience, a significantly higher budget will be required to develop a more aggressive program. I am pleased to know that you may soon have the funds so that we would not have to delay the work any further.

Dr. Burzynski, I hope to meet with you in the near future to discuss the research protocols in depth. Also, I should mention that I plan to be in Europe in October; should you find it appropriate, I will be glad to make arrangements to meet with your colleagues at the Sigma-Tau institute in Italy. I am looking forward to collaborating with you on this exciting project.

Sincerely yours,

Dvorit

Dvorit Samid, PhD
Assistant Professor of Pathology