THE CANCER LETTER

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LEDERBERG APPOINTMENT AS PANEL CHAIRMAN CONFIRMED; BERNARD FISHER WILL BE NAMED TO THE OTHER VACANCY

The White House finally has made it at least semiofficial—Joshua Lederberg, Nobel laureate and president of Rockefeller Univ., will be the new chairman of the President's Cancer Panel. The other vacant position on the Panel will be filled by Bernard Fisher, professor of surgery at the Univ. of Pittsburgh and chairman of the National Surgical Adjuvant Breast & Bowel Cancer Project.

It has been no secret for months that Lederberg was the choice of

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In Brief

REORGANIZATION PACKAGE WENDING ITS WAY THROUGH THE BUREAUCRACY; FDA SEEKS NAMES FOR COMMITTEE

NCI'S REORGANIZATION package, nearly two years in the making, has finally been sent up through channels to the HEW secretary. Everyone along the way has been unable to resist getting in his licks, from NIH to the assistant secretary for health office; no bureaucrat worth his salt will pass up an opportunity to nitpick. It will be months before approval trickles down. In the meantime, NCI is stuck with the old and irrelevant organizational status and division names. To avoid confusion, ***The Cancer Letter*** henceforth will use the new names—the Div. of Extramural Activities (DEA), replacing the Div. of Cancer Research Resources & Centers; and the Div. of Centers, Community Activities and Resources (DCCAR), replacing the Div. of Cancer Control & Rehabilitation. We also will use the new department initials—HHS, for HEW (Health & Human Services). . . . **SHELDON SAMUELS**, member of the National Cancer Advisory Board, reflecting the opinion of many toward White House budget makers: "If you applied zero based budgeting to OMB, would we still have an OMB?". . . . **NUTRITION IN CANCER** Conference sponsored by the Univ. of Wisconsin Clinical Cancer Center is scheduled for Dec. 7 in Madison. Topics include nutritional needs of cancer patients, cancer malnourishment and nutritional evaluation, impact of nutrition on immunologic evaluation. . . . **FOOD & DRUG** Administration is seeking nominations to fill vacancies on several of its advisory committees, including two that will be open on the Oncologic Drugs Advisory Committee next June. The terms of Richard McHugh, professor of biometry at the Univ. of Minnesota, and John Whitaker, medical oncologist and hematologist in private practice at Austin, Tex., expire then. . . . **NATIONAL TOXICOLOGY** Program has scheduled a public meeting for Dec. 3 at the NIH Masur Auditorium to discuss preliminary results from the international program to evaluate short term tests for carcinogenicity. The study is attempting to compare the capability of 30 assay systems to correctly differentiate between known carcinogens and noncarcinogens. The meeting will be held from 9:30 a.m. to 12:30 p.m.

LEDERBERG SAYS HE'S "ENTHUSIASTIC" ABOUT CANCER PROGRAM, PREVENTION

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former HEW Secretary Joseph Califano to succeed Benno Schmidt as Panel chairman. But Panel members are Presidential appointees, and before President Carter could get around to acting on Califano's recommendation, he fired Califano. The recommendations went back to HEW for new Secretary Patricia Harris' consideration.

Carter still has not formally made the appointments. But Gilbert Omenn, assistant director for human resources in the White House Office of Science & Technology Policy and an ex officio member of the National Cancer Advisory Board, revealed the impending appointments at Monday's meeting of the Board.

The identity of the other appointee, to fill the seat formerly held by Columbia Cancer Center Director Paul Marks, was less well known. Fisher's selection will be well received in most quarters, although he is a controversial figure among the more traditionalists in the breast cancer field.

Lederberg's reign promises to be considerably different than that of his predecessor. Schmidt was on good terms with the man who appointed him, Richard Nixon, at least in the first year or two after the Panel was established. Schmidt used that influence with Nixon and later with Gerald Ford to gain access to the White House policy makers, including the President on occasion. Nixon accepted the Panel's recommendation to make Frank Rauscher director of NCI in 1972. It was heat from Schmidt and fellow Panel members, along with pressure from Congress, that got the Nixon Administration to back down on its attempt to kill federal support of research training, although it was cut back severely for a while.

Lederberg probably will have no such entree to the White House. Carter has turned over selection of Presidential appointees such as NCI director, Panel members and NCAB members entirely to the HEW (now HHS) secretary, contrary to the intent of the National Cancer Act.

Lederberg told ***The Cancer Letter*** that he had one brief conversation with Califano and has not yet met Harris, although he was to have had a meeting this week with Julius Richmond, assistant secretary for health. Lederberg does not feel, however, that his lack of clout with the President will prevent him from being effective in his new role.

"There were certain elements of personal involvement in the past which will not be present now," he said. "There is still a role to be filled. It may not be so important now to reach the President as it is to get to the American people and to Congress."

Lederberg was reluctant to discuss the Cancer Program as Panel chairman, with the appointment still not formally made. He said he did feel free to express his views as a private citizen and scientist.

"The fact is, I've not given close attention to cancer research in the last six or seven years. I'm starting with a completely fresh view. I have lots of homework to do, to bring myself up to-date. I have no fixed commitments."

Lederberg recalled that he served on the Yarborough Panel whose recommendations led to passage by Congress of the National Cancer Act of 1971. "I agree that an accelerated effort in cancer research was desirable, but I was not enthusiastic about building new structures. I felt NIH provided an adequate framework for the increased effort we proposed (the Yarborough Panel had recommended that NCI be split away from NIH and operate as an independent agency).

"There were promises made then which I didn't adhere to. But I remain very enthusiastic about the Cancer Program. I tend to agree with those who feel we have more to gain in the prevention area than we do in looking for cures. In the meantime, we will continue to have a lot of people suffering acutely from cancer. As unsatisfactory as the therapeutic approach has been, we need to continue to try to improve it.

"I would like to see people who are working on various aspects of cancer converge more often. I have never felt that medical progress goes in a linear fashion. Medicine is more complicated than that. Research in basic science can be inspired and invigorated by clinical observations. People with different perspectives can be motivated and helped to progress through more variety in approaches."

The NSABP (the bowel cancer component was only recently added) under Fisher's leadership was one of the pioneers in the adjuvant chemotherapy studies which have been responsible for much of the progress in treatment of breast cancer. Fisher had to challenge prevailing theories of the disease and ran into tremendous opposition from many of his surgeon colleagues. Not only have his studies led to development of combination chemotherapy for breast cancer; one study demonstrated that more conservative surgery resulted in disease free and survival rates comparable to the long established Halsted radical mastectomy. Although that finding is being questioned by many surgeons, it formed the basis for the NIH consensus that total mastectomy with axillary node dissection should be the standard treatment for stage 1 and selected stage 2 breast cancer.

Fisher, who insists that no clinical study is worth doing unless it asks biological questions, feels his studies have demonstrated that breast cancer is a systemic disease, probably from its inception, and is disseminated through the blood stream. This is in direct conflict with the long accepted theory that the disease spreads from the tumor in the breast through the lymphatic system. Surgery therefore is necessary only for local control, Fisher contends.

NSABP is presently conducting a study to deter-

mine if segmental mastectomy plus node dissection is equivalent to total or radical procedures in disease free interval and survival. If it is, that would further reinforce Fisher's views of the biology of breast cancer.

UPTON DECLINES TO DISCUSS DEPARTURE; DEVITA APPOINTMENT APPEARS LIKELY

Arthur Upton passed up the opportunity to discuss his impending departure from NCI with the National Cancer Advisory Board Monday during his report to the Board. He later told ***The Cancer Letter*** he was still "under constraints," referring to the Administration's orders to him.

Asked if those constrains still were in effect when the time came for him to leave (the guesses range from Dec. 15 to 31), would he steal away quietly in the night, the NCI director laughed and said, "I just don't know."

The gag order not only is silly, it is superfluous. The fact that Upton will become director of NYU's Institute of Environmental Medicine, replacing Norton Nelson, is one of the world's worst kept secrets.

Meanwhile, it appears more likely than ever that Div. of Cancer Treatment Director Vincent DeVita will at least be named acting director when Upton leaves, with the possibility that HHS Secretary Patricia Harris will recommend to President Carter that DeVita be given the permanent appointment.

DCT BOARD'S PROPOSALS FOR DEVELOPING THYMOSINS IN SUBCOMMITTEE'S REPORT

The proposals for development of NCI's Biologic Response Modifiers Program which were adopted by the Div. of Cancer Treatment Board of Scientific Counselors appeared in part in the Nov. 9 issue of ***The Cancer Letter,*** with the plans for interferon and chemoprevention.

Following is the proposal for thymosins, as described in the report of the Board's Subcommittee on Biologic Response Modifiers:

The projects proposed for the development of thymosins fall into three major categories:

a) Clinical trials and related studies.

b) Basic developmental research.

c) Production.

Major support will be provided in terms of material production by Hoffmann LaRoche Inc., which has an active program for the development of thymosins. Thymosin fraction 5 and a_1 would be provided by that pharmaceutical group free of charge for study under the aegis of the BRM program.

Clinical trials and related studies. It is recommended that phase 1 trials of both thymosin fraction 5 and a_1 be carried out during the first year of the program, and that phase 2 trials be initiated only when a regimen can be designed using doses proven in the course of the phase 1 trials to have restorative capabilities with respect to T cell numbers and function. Accordingly, whether phase 2 trials could be initiated during the first year will depend on the speed of acquisition of information from phase 1 trials.

Phase 1 trials: Since thymosin acts in an immunorestorative manner rather than having a direct antitumor effect, a primary prerequisite for initiation of clinical trials should be documented immunosuppression, due either to the direct presence of the tumor or the therapeutic regimen, i.e. chemotherapy, radiotherapy, and/or surgery. Responsiveness to thymosin would require that there be some bone marrow reserve and the presence of thymosin responsive cells in the blood (in vitro assay). An appropriate trial setting would be measuring the capacity of thymosin to reconstitute or maintain T-cell immunity in immunoincompetent cancer patients. Three trials with thymosin fraction 5 and three trials with thymosin a_1 should be carried out for a total of six studies.

The selection of particular malignancies for phase 1 trials is based on data which suggest that patients with these diseases have marked depression of immunologic reactivity and therefore could have measurable restoration of immunologic competence on immunologic monitoring during the phase 1 trial. The assays to measure restoration of immune competence using peripheral blood lymphocytes should be chosen from among those listed below: 1) measurement of T-cell numbers and subpopulations using rosette assays with and without thymosin present: a) total rosettes; b) $T\mu$ and $T\gamma$ subpopulations. 2) measurement of peripheral blood lymphocyte T cell and $T\mu$ and $T\gamma$ cell functional responsiveness in vitro with and without thymosin present, using: a) mixed lymphocyte reaction; b) mitogen responses; c) antibody production in response to pokeweed antigen.

Phase 1 studies should also include pharmacologic evaluation of the kinetics of thymosins, i.e. serum and tissue half life. Radioimmunoassays or ELISA assays for the polypeptide factors will be used as they are developed. When those assays are not available, serum levels will be quantitated by bioassay using the murine azathioprine rosette assay of Bach and/or the murine Thy-1 assay of Twomey. Radioimmunoassays are already available for some of the thymic peptides such as thymosin a_1 and thymopoietin.

Phase 1 trials of thymosin fraction 5 and thymosin a_1 should be done over a dose range to determine the optimal reconstitutive dose. A reference dose would be 60 mg/M^2 because this appears to be active in immunodeficiency diseases and in an initial therapeutic trial in patients with oat cell carcinoma of the lung. A schedule should be devised to achieve maximum immunorestorative effects. An adequate number of patients at each dose and schedule level to define biological activity is needed. Concurrent randomized controls not receiving thymosin fraction 5 and thymosin a_1 are mandatory because of the variations in

human immune reactivity. Studies should be done first in patients not on other therapy but subsequently could be done in patients on cytoreductive therapy. Trials with thymosin a_1 would be similar except the reference dose would be 0.6 mg/M^2 as suggested by initial results of clinical tests.

Therapeutic trials with thymosin fraction 5 and thymosin a_1. These studies would be conducted in tumor bearing patients as well as in those who are clinically disease free but at high risk for recurrence. Patients should be immunoincompetent at the initiation of therapy or likely to become immunoincompetent as a result of their therapy or their disease. In tumor bearing patients randomization would be between conventional therapy alone or in combination with thymosin. The end points of these trials would be therapeutic efficacy (i.e., objective response rates, remission duration, survival, etc.) and immunorestorative efficiency. Disease free patients should be randomized between thymosin (or thymosin containing) maintenance regimens and appropriate control(s). Again the end points would be therapeutic efficacy and immunorestorative efficiency.

Basic developmental research. Further studies with components of thymosin fraction 5, as well as comparative evaluation and development of other known thymic factors which may offer additional selective therapeutic advantages, are recommended. The thymic factors that have been reported, in addition to the thymosins, to give significant biological activities include thymic humoral factor (THF), factor thymique serique (FTS), thymopoietin, thymic factor (TF) and the pre-albumin thymosin-like factor. An additional number of factors have been reported which may prove to be, in the future, clinically useful.

Thymosin Fraction 5 and Its Component Peptides

1. Study of the role of thymosin in stem cell differentiation, maturation and function. a) Induction of markers: Initial studies have demonstrated that several of the thymic preparations influence expression of T-cell markers and functions in some marrow stem cell populations. Now that purified and synthetic thymic peptides are becoming available, these preparations should be investigated in terms of their potential to induce T-cell differentiation in purified stem cell subpopulations. Amongst the criteria for T-cell differentiation would be (1) appearance and disappearance of T-cell specific markers, e.g. in mice, TdT, 20*a*SDH, Thy-1, Lyt, TL, Qa, etc., and in humans HTLA, TdT, autologous rosette $T\gamma/T\mu$ ratio, etc.; and (2) the appearance and disappearance of these markers should correlate with functional properties, e.g. regulation of T-cell helper and suppressor function, reactivities in MLR and antibody forming assays.

Emphasis should now be placed on the biochemical events leading to stem cell differentiation. Analysis of surface membrane and intracellular metabolic and enzymatic changes, resulting from exposure to thymic hormones, and resulting in evidence of T-cell differentiation, should be performed, e.g. induction of cyclic nucleotides, alterations in Ca^{++} transport, changes in protein synthesis, etc.

It is important that the various thymic peptides, such as the components of thymosin fraction 5, be studied in sequence and in combination in order to analyze the maximum potential for induction of stem cell differentiation along the T-cell pathway. Utilization of procedures, such as fluorescence activated cell sorting (FACS), to isolate stem cell subsets at different stages of differentiation will be helpful in elucidating the effects of thymic peptides.

It is likely that several peptides may act on different stem cell subsets in multiple stages to induce different T-cell pathways. Since many of these studies can and should be carried out in vitro, these approaches should be conducted with both human and animal cell models.

b) Induction of functional T-cells. The thymosins should be studied for their capacity to induce functional alterations in lymphocyte reactions that can be explained by lymphocyte maturation. Special emphasis should be given to restoring defective lymphocyte function in vitro in cancer patients and in vivo and in vitro in tumor-bearing animal systems. Assays that should be utilized include: (1) the mixed lymphocyte reaction, including modification of the reactivity of peripheral blood lymphocytes from tumor-bearing patients or animals and of purified T-lymphocyte precursors; (2) the production of lymphokines such as MIF in response to antigens using thymectomized animal models or lymphocytes from cancer patients; (3) the suppression or regulation by T-cells of immunological reactions to tumor cells, allogeneic cells or mitogens; (4) the development and modulation of cell-mediated cytotoxicity reactions to tumor, allogeneic and synergeneic cells and antibody responses.

2. Role of thymic hormones in normal differentiation and maturation of functional T-cells. In vivo, the thymus most likely functions at a minimum of three levels: (1) inducing differentiation of incoming stemm cells to form immature thymocytes; (2) inducing immature T-cells to become mature T-cells in the thymus; and (3) inducing maturation in the periphery by elaborating circulating thymic hormone(s). There is a major need to establish the full role of the thymic hormones in stem cell development. A second important area of basic research is the question of how thymic peptides act in situ in the thymus, and how and where hormonal synthesis is regulated.

Priority areas of research should include: (1) identity of the (epithelial) origins of the various thymic hormones, either by fluorescence or radioautographic techniques, utilizing antibodies raised against the thymosin peptides. Studies with cultures of thymic epithelial cells of animal and human origin will be

useful in these studies. Questions such as the homeostatic control of hormonal synthesis need to be addressed, e.g. how the other endocrine organs influence thymic epithelial function and synthesis of thymic hormones. Consideration should also be given to the influences of ontogeny, senescence and clinical states on such function and synthesis. Attention should also be directed to thymic epithelial function and control in abnormal states such as thymomas (e.g. human, or murine (AKR) where thymic epithelial malfunction may be a key component to the pathogenesis of lymphoma).

(2) Further information is needed on the influence of thymic hormones and individual peptides on thymocyte subpopulations, and the intrathymic differentiation pathways. Cell separation procedures, such as binding to peanut lectin agglutinin, FACS, sensitivity to steroids, etc. can be used as experimental approaches. The same criteria for T-cell differentiation and function, as described for stem cell studies above, can be used to evaluate mechanisms of thymic peptide action. Again, studies with human and animal cells are desirable.

Since the thymus functions as an endocrine organ, more basic research is needed on the levels and forms of thymic hormones (precursors, degradation products) in the circulation, as well as on the peripheral target cells of the circulating products. Analysis of peripheral lymphoid cell subpopulations, by the same criteria described above (i.e. differentiation as judged by biochemical, antigenic and functional markers of T-cell differentiation) are needed.

(3) Influence of the thymosins on states of immune imbalance. Ultimately, the basic research on thymic hormones should lead to therapeutic applications in clinical disorders with immunological components. Amongst the areas in which more basic research is needed are: (a) tumor growth, (b) autoimmune disorders, (c) aging, and (d) infectious diseases. Above mentioned research on stem cells and thymocyte differentiation and maturation will also be directly applicable to the understanding and treatment of the primary and secondary immunodeficiencies. Conversely, understanding of how thymic hormones function in states of immune imbalance should provide insights into the basic mechanisms of action of thymic hormones in the maintenance of normal immune balance and in host resistance to progressive tumor growth.

Tumor growth. Solid tumor models which will allow the analysis of how thymic hormones influence helper and suppressor functions in experimental conditions of tumor growth and regression are needed. Analysis of T-cell subpopulations such as cytotoxic T-cells, K cells and others should be included.

Autoimmune disorders. Thymic hormones may act in autoimmune disorders with opposite effects to that seen in immunodeficiencies. In immunodeficiencies, there is often a deficit of helper cell activity. In some autoimmune disorders, evidence suggests a deficit of suppressor cells. A key area for investigation is the effect of thymic hormones on regulation of immune responses directed against self antigens, with particular attention to suppressor cell subpopulations. Thus, humoral and cell-mediated models of modified-self immune responses, as well as specific investigation of autoimmune disease models, e.g. experimental arthritis, NZB disease, are needed. Analysis of thymic epithelial function in such disease states will also be helpful.

Aging. Many of the studies on autoimmunity are also appropriate to aging, as these two conditions often go hand-in-hand. Specifically, however, areas of thymic hormone research in aging should be directed to: (a) analysis of stem cell and thymocyte subpopulations, and their responsiveness to thymic hormones as a function of age (humans and animals). (b) Analysis of thymic epithelial function and homeostatic regulation thereof, as a function of age. (c) Analysis of peripheral T-cells (helper and suppressor) and the influence of thymic hormones on the function and balance of these T-cell subpopulations as a function of age. (d) Analysis of the mechanisms of host resistance to progressive tumor growth with age and the role of thymic hormones in modulating resistance.

Infectious Diseases: Increased susceptibility to viral, mycobacterial and fungal pathogens in cancer patients due to severe immunosuppression is a major problem. Analysis of the capacity of the thymosins to increase resistance to pathogenic organisms should be studied in a variety of animal models.

4. Biochemical Characterization and Synthesis of Thymic Peptides.

Considerable progress has been made in the past two years in the chemical characterization of several of the biologically active purified thymosin peptides, as well as with the active biological components of THF, thymopoietin II, and the serum thymic factors of Bach (FTS) and Astaldi (SF) and other thymic derived or dependent factors, such as the pre-albumin fraction of White. Given a potential role for these thymic factors in modulating immunity, a major area for priority development would be the support of research proposals to fully characterize chemically the biologically active polypeptides. These studies should include purification of material in sufficient quantities for amino acid sequence analysis.

There is also a major need to develop capabilities of using new techniques such as high performance liquid chromatography (HPLC) and preparative isoelectric focusing (IEF) for the separation and sequence studies of the thymosin polypeptides. Many of the thymosin polypeptides have similar physical-chemical properties such as size and charge. The development of new techniques utilizing HPLC and preparative IEF would add great strength to the conventional column chromatography techniques presently

available and are necessary to achieve separation of all components in thymosin fraction 5.

Sequence analysis of the purified polypeptides is necessary as it will facilitate comparison and the identification of similar to disparate biologically active components in the various thymic preparations. Major efforts should be given to the synthesis of biologically active and well-characterized thymic polypeptides in order to develop the methodology necessary for large scale production geared to clinical applications. Classical chemical synthesis and solid phase synthesis of thymosin a_1, thymopoietin II and FTS have already been accomplished. Similar strategies should be developed with the other thymic factors.

5. Development of Assays to Measure Levels of Thymosins in the Blood

The development of sensitive radioimmunoassays or ELISA assays of the thymosin peptides in the blood are needed to identify patient populations and to monitor therapy.

Studies with Other Thymic Factors

Studies, such as those outlined above for the thymosin polypeptides, should also be carried out in a similar manner for thymic humoral factor (THF), factor thymique serique (FTS), pre-albumin thymic factor, thymopoietin II, and other thymic factors (as they are identified). It is essential that adequate material of each of these factors be made available to the basic immunobiology research laboratories working in this area so that comparisons between the different factors can be made.

Production

Based on the studies proposed, it is estimated that approximately 5,000 gms of thymosin fraction 5 and 62 gm of thymosin a_1 will be required and will be used as follows:

Thymosin fraction 5	
Phase 1	942 gm
Therapy trials	3,767 gm
Research and development	200 gm
Total	**4,909 gm**
Thymosin a_1	
Phase 1	9.42 gm
Therapy trials	50.30 gm
Research and development	2.00 gm
Total	**61.72 gm**

Support Recommendations

Support is recommended (1) for the clinical trials, (2) for the development of clinical resource laboratories which can carry out the immunological analysis required for these trials, and (3) for laboratories which are capable of providing the various thymic preparations and radioimmunoassays for the necessary research activities, and for carrying out important aspects of the basic research program, such as preparation and testing of thymosin fraction 5 components (other than thymosin a_1); development of radioimmunoassays for thymosin peptides and screening of blood samples in the phase 1 and phase 2 trials; preparation of pre-albumin thymic-like compounds; preparation of THF, SF, STF and thymopoietin for comparative studies; comparative screening of thymic hormones in defined animal models of immunosuppression; and development of novel approaches for large scale production of clinically defined thymic hormones.

The Board's recommendations for other areas of the Biologic Response Modifiers Program will be reported in future issues of ***The Cancer Letter.***

NCI ADVISORY GROUP, OTHER CANCER MEETINGS FOR DECEMBER, JANUARY

Clearinghouse on Environmental Carcinogens Chemical Selection Subgroup—Dec. 3, NIH Bldg 31 Rm 4, 9 a.m., open.
National Toxicology Program—Dec. 3, NIH Masur Auditorium, 9:30 a.m., discussion of preliminary assessment of international survey of short term carcinogenesis tests, open.
4th Annual Asian Cancer Congress—Dec. 4-8, Bombay.
Pacific Endocurietherapy Society—Dec. 5-7, Mazatlan.
Critical Issues in Toxicology & Environmental Health—Dec. 5-7, Sheraton Park Hotel, Washington D.C.; American College of Toxicology and Mt. Sinai School of Medicine.
Bladder Cancer Review Committee—Dec. 6-7, Logan Airport Hilton, Boston, open Dec. 6, 8:30–9 a.m.
Large Bowel Cancer Review Committee—Dec. 6-7, Prudential Bldg., Houston, open Dec. 6, 7:30 p.m.- 8 p.m.
Nutrition in Cancer—Dec. 7, Univ. of Wisconsin Clinical Cancer Center, Auditorium G5/119, Madison, 9 a.m.
Clinical Cancer Program Project Review Committee—Dec. 10-11, NIH Bldg 31 Rm 6, open Dec. 10, 8:30–10:30 a.m.; open 4 p.m.–adjournment for discussion of bone marrow transplant research.
Cancer Control Merit Review Committee—Dec. 12-14, NIH Bldg 31 Rm 8, open Dec. 12, 9–9:30 a.m.
Cause & Prevention Scientific Review Committee—Dec. 14, NIH Bldg 31 Rm 6, open 9–9:30 a.m.
Cancer Control Intervention Programs Review Committee—Dec. 14, Kenwood Country Club, Bethesda, open 8:30–9 a.m.
New Drug Seminar—Dec. 17-18, NIH Masur Auditorium, 8:30 a.m., open (asparaginase and daunorubicin).
Second Workshop on Cloning Human Tumor Stem Cells—Jan. 3-5, Univ. of Arizona, Tucson.
National Cancer Advisory Board—Jan. 21-23, NIH. Hours and subcommittee schedules will be published in Jan. 4 issue.

Additional January meetings will be published in the Jan. 4 issue of ***The Cancer Letter.***

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute, unless otherwise noted. Write to the Contracting Officer or Contract Specialist for copies of the RFP, citing the RFP number. Some listings will show the phone number of the Contract Specialist, who will respond to questions. Listings identify the respective sections of the Research Contracts Branch which are issuing the RFPs. Address requests to the contract officer or specialist named, NCI Research Contracts Branch, the appropriate section, as follows:
Biology & Diagnosis Section and Biological Carcinogenesis & Field Studies Section—Landow Building, Bethesda, Md. 20205; Control & Rehabilitation Section, Chemical & Physical Carcinogenesis Section, Treatment Section, Office of the Director Section—Blair Building, Silver Spring, Md. 20910. Deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP NCI-CP-FS-01015-75

Title: *Support services for studies of immunological and immunogenetic determinants of high-risk cancer families*

Deadline: *Approximately Jan. 3, 1980*

The Environmental Epidemiology Branch, Div. of Cancer Cause & Prevention of NCI is seeking professional and technical support for its family studies program. This will be a support, not a research, contract.

Prospective contractors must have experience and expertise in all phases of immunologic and immunogenetic testing, such as performance of in vitro blastogenesis assays to mitogens, antigens, and allogeneic lymphocytes; quantitative assays of various lymphocyte subpopulations, migration inhibition, and other assays of immune function; and other types of tests of immune function, immunogenetic, and immunoregulatory function that might prove useful in evaluation of high-risk families.

In addition, prospective contractors must have the capability for preparing a variety of specimens for storage under optimum conditions, including white blood cells and various subpopulations, red blood cells, serum, plasma, tumor tissues and extracts, urine, body fluids, stools, and other biologic materials relevant to the conduct of family studies research which is being undertaken by NCI personnel.

Contractors should also have capability to establish lymphoblastoid cell lines on selected family members and will store these cell lines under optimum conditions. Other duties will include the following: (a) Picking up, taking, or collecting biologic specimens from a variety of locations as directed, involving local or air travel within and outside normal working hours; (b) preparing specimens for storage as requested by protocols, if not immediately utilized or tested; and (c) conducting the cited tests on biologic specimens obtained from members of high-risk cancer families in and outside the Washington area.

Key personnel will include a principal investigator (20% of time or more) having a PhD or equivalent degree, with proven expertise in the field of cellular immunology and immunogenetics as reflected by prior and current publications in reputable scientific journals dating back at least two - four years. The principal investigator shall work closely with Family Studies professionals in the EEB, in the development of study protocols employing the latest advances in the field of immunology/immunogenetics to test etiologic hypotheses. Other personnel will include an associate immunologist (100% time) with PhD or equivalent degree and other technical staff and computer support personnel to achieve the contract objectives.

The contractor must have or be willing to establish, prior to award of contract, permanent offices and complete laboratories within 50 miles of the NIH off-campus Landow building, 7910 Woodmont Ave., Bethesda, Md. 20205, in which the Environmental Epidemiology Branch of NCI is located. It is mandatory that the contractor shall have on hand the necessary laboratory equipment to conduct the necessary tests.

Contract Specialist: Karlene Wakefield
Biological Carcinogenesis & Field Studies
301-496-1781

RFP NCI-CP-FS-01011-77

Title: *Support services for radiation studies*

Deadline: *Jan. 30*

Environmental Epidemiology Branch, Div. of Cancer Cause & Prevention, NCI, is seeking technical (non-professional), managerial, and clerical support for its radiation studies program.

Prospective contractors must have experience and expertise in all phases of radiation studies, such as, the design of data collection documents, abstracting, interviewing, keying and editing of data, recoding, tracing of members of established cohorts, procuring death certificates, creation and manipulation of computer files, and generation of basic statistics.

Personnel required include six fulltime permanent persons (1 data collection manager, 1 assistant data collection manager, 1 programmer/analyst, 2 computer programmers and 1 clerk/typist) and 8 person-years of part-time help. The contractor must have or be willing to establish, at time of submission of a proposal, permant offices within 50 miles of the NIH off-campus Landow building, 7910 Woodmont Ave., Bethesda, Md., in which the branch is located.

A mandatory requirement for Small Business subcontracting is included in this RFP.

Contract Specialist: Patrick Williams
Biological Carcinogenesis & Field Studies
301-496-1781

RFP N01-CM-07300-14

Title: *Large scale isolation of antitumor agents from natural sources*

Deadline: *Approximately Jan. 25*

NCI's Div. of Cancer Treatment will make available to interested contractors a request for proposals concerning a project to extract, isolate, and purify antitumor agents from plant and animal materials on a pilot plant scale. The contractor must provide a pilot plant facility capable of storing up to 50,000 lbs and processing up to 20,000 lbs of bulk crude material and must have experience in process development of natural products isolations. The government will supply the plant and animal materials to be processed. The contractor will supply all equipment, solvents, reagents, and other materials needed for the project. It is planned that one contract will be awarded for an incrementally funded three-year peri-

od of performance. It is anticipated that a cost reimbursement type contract will be awarded requiring a level of approximately 5 man-years per year.
Contract Specialist: Susan Hoffman
Treatment
301-427-8737

RFP N01-CM-07303-14

Title: *Development and production of pharmaceutical dosage forms*
Deadline: *Approximately Jan. 11*

NCI requires a pharmaceutical facility for the development of pharmaceutical dosage forms of potential antitumor agents. Development activities will be directed toward sterile freeze dried injected dosage forms for use in preclinical toxicological evaluation and subsequent clinical trial in man. Most production assignments will require preparation of 4,000-6,000 freeze dried units per batch. Chemical, physical and biological testing is required on all batches. Shelf life surveillance will be required on most lots. Organizations must submit evidence of experience in production and development of freeze dried dosage forms, plus possess adequate resources to meet project requirements.
Contract Specialist: Susan Hoffman
Treatment
301-427-8737

RFP N01-CM-07304-15

Title: *Development of parenteral dosage forms for clinical investigation*
Deadline: *Approximately Jan. 11*

Pharmaceutical Resources Branch, DCT, needs the services of an organization with demonstrated expertise involving development of intravenous dosage forms of poorly water soluble antitumor agents. Investigations will be directed toward resolution complex solubility and/or stability problems associated with certain potential antitumor agents. Pilot scale formulation batches (50-100 units) will be required for independent evaluation of the formulation approach. Organizations must submit evidence of in-house competence and experience in pharmaceutical development of intravenous dosage forms. Emphasis will be placed on awareness of the problems and approaches to their resolution.

It is anticipated that an incrementally funded contract will be awarded for a period of three years at a level budget. Each increment will be for a period of one year. Responders are required to submit proposals for two levels of effort. The first year technical man years of effort of two and three years, respectively, with 5% annual reductions in technical man years for the subsequent periods.
Contracting Officer: John Palmieri
Treatment
301-427-8737

RFP NCI-CM-07299

Title: *New fermentation antineoplastic drug acquisition, evaluation, development and screening*
Deadline: *Approximately Jan. 15*

NCI's Div. of Cancer Treatment will make available to interested contractors an RFP for new fermentation antineoplastic drug acquisition, evaluation, development and screening. Contractor must provide and operate a biochemical, biological fermentation laboratory with a pilot plant facility to produce and isolate potential antineoplastic antibiotics. It is anticipated that three contracts will be awarded for a three year incrementally funded period of performance.

Candidate organizations must show evidence of experience in all phases of fermentation (shake flask, stir jar, pilot plant), in vitro screening, as well as the expertise to accomplish fermentation optimization studies, chemical isolation, purification and structural characterization of potential antitumor antibiotics produced by routine fermentation and the proper maintenance and preservation of active cultures. This work will require that a minimum of 2,000 unusual organisms be obtained and evaluated under various fermentation conditions and on many different substrates. The successful contractors must also have the resources and ability to produce, isolate and purify antineoplastic material from large-scale fermentations. In addition, those who wish may propose on optional research and development work necessary to support the primary project. These options include: in vivo assays to speed up primary screening and monitor fermentation optimization studies; the development of suitable dosage forms for new agents and the preparation of clinical amounts of active antitumor compounds with safety and quality control tests; and biochemical characterization studies. The level of effort required for the primary research during the three-year contract period: year 1: 14 staff years; year 2: 13 staff years; year 3: 12 staff years.

The optional work described will require three to nine staff years for completion.
Contract Specialist: Sandra Antony
Treatment
301-427-8737

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