THE CANCER LETTER

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DCCP BOARD OKAYS NEW PROJECTS IN CHEMOPREVENTION, OTHER PROGRAMS TOTALING $5 MILLION IN FIRST YEAR

The Board of Scientific Counselors of NCI's Div. of Cancer Cause & Prevention has approved the concept of more than $5 million a year in new research and resource contract supported projects, including:

- Five contracts, some of which may include multiple awards, for chemoprevention development, mostly involving retinoids. Awards for the first year (fiscal 1981) are estimated to total $2,170,000.
- Another related project involving suppression or reversal of malignancy, with an estimated $500,000 first year cost, to start a systematic search for substances that will "significantly modify the malignant phenotype."
- A five year contract for development of a woodchuck hepatoma model, at a cost of $250,000 for the first year, to follow up on the

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In Brief

PRESIDENT'S REQUEST FOR NCI FY 1981 BUDGET: SAME AS 1980; NEW CLINICAL STUDY SECTION OPTION OPEN

NCI'S FY 1981 budget that will be in the President's budget message to Congress in January will be $1 billion, the same amount the Cancer Program is getting in the current fiscal year. NCI had requested $1.17 billion, so the struggle this year will be over the $170 million difference. With inflation, NCI will need a minimum of $100 million more just to stay even. . . . **WILL NIH** charter a new study section to review clinical research grant proposals? NCI Div. of Cancer Treatment Director Vincent DeVita said that the NIH Div. of Research Grants is doing further analysis on a survey which tends to corroborate suspicions of many clinical investigators that clinical trials grant applications do not fare well with existing study sections. . . . **ANN BLUES**, acting deputy director of the Ephraim McDowell Community Cancer Network in Kentucky, has been elected president of the National Hospice Organization. Robert Brown, St. Paul, Minn., M.D., is president elect, and Time Inc. managing director Zachary Morfogen is chairman of the board. . . . **HILDA WEXLER**, biologist in the Surgery Branch of DCT's intramural Clinical Oncology Program, has received the John F. Fenney Memorial Service Award from the D.C. Div. of the American Cancer Society. . . . **FRED SANGER**, English Nobel Laureate, will deliver the keynote address at the 12th Annual Miami Winter Symposium Jan. 7-11. Theme of the symposium is "Mobilization and Reassembly of Genetic Information." Other speakers include Stanley Cohen and Paul Berg of Stanford, Howard Goodman of the Univ. of California (San Francisco), Peter Starlinger and Hans Saedler of West Germany, and Maxine Singer of NCI's Div. of Cancer Biology & Diagnosis. The symposium is sponsored by the Papanicolaou Cancer Research Institute and the Univ. of Miami Dept. of Biochemistry.

DCCP BOARD APPROVES RECOMPETITION OF CONTRACTS, INTERAGENCY RENEWALS

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recent finding that the eastern woodchuck harbors a virus similar to the human hepatitis B virus.

• A three year project, with an estimated cost of $1 million for the first year, for studies of the nutritional and other in vitro requirements of cultured human epithelial cells.

The DCCP Board also approved the recompetition of four information resource projects costing about $2 million a year, and went along with renewal of interagency agreements with the National Institute of Occupational Safety & Health and the Environmental Protection Agency.

Finally, the Board agreed to an EPA proposal for a joint project to study interspecies relationships in metabolism, pharmacokinetics and toxicities.

The projects as described by DCCP staff:

Synthesis of new retinoids for chemoprevention of epithelial cancer—Proposed first year award, $600,000, four years.

Retinoids (vitamin A and its synthetic analogues) control cellular differentiation in epithelia of many target tissues, including bronchi and trachea, uterus, prostate, kidney and bladder, stomach, intestines, pancreatic ducts, breast, and skin. Large numbers of synthetic retinoids have been made, in which there has been substantial modification of the ring, side chain, or polar terminal group of the natural vitamin A molecule. Several synthetic retinoids can prevent the development of epithelial cancer of the skin, respiratory tract, mammary gland, and bladder in experimental animals. Moreover, retinoids can suppress malignant transformation of 10T 1/2 cells in culture induced by chemical carcinogens or γ-radiation, and further are capable of blocking phenotypic cell transformation produced by sarcoma growth factor. Practical application of these findings for prevention of cancer in people will depend on further synthesis of new retinoids having more desirable pharmacological properties, such as greater potency, less toxicity, or better pharmacokinetic properties. The Chemical/Physical Carcinogenesis Branch proposes to continue ongoing efforts for synthesis of new retinoids. Continuation of these efforts will provide continuity to ongoing studies aimed at developing more desirable retinoids for long-term studies of inhibition of carcinogenesis.

Synthesis of radiolabeled retinoids for metabolic and pharmacologic studies in chemoprevention of cancer—Proposed first year award, $600,000, four years.

These efforts will provide continuity to ongoing studies aimed at facilitating basic research on the biochemistry and pharmacology of these compounds by making available radioactive retinoids for studies on the biochemical pathways of retinoid metabolism, including studies of retinoid binding proteins, as well as pharmacokinetic studies of absorption, distribution, biotransformation and excretion. Such investigations are critically needed for an understanding of the mechanism(s) of action of retinoids in the inhibition of carcinogenesis and malignant transformation, and for a rational approach to the design of more efficacious retinoids.

Synthesis and procurement of substances in support of research on chemoprevention—Proposed first year award, $50,000, four years.

Since there are compounds other than retinoids which appear to have promise for chemoprevention, the Chemical/Physical Carcinogenesis Branch wishes to begin a small project on the synthesis and procurement of substances (e.g., radiolabeled phenolic antioxidants, protease inhibitors, etc.) in support of research in chemoprevention.

Bioassay of retinoid activity by tracheal organ culture system—Proposed first year award, $300,000, three years.

As new retinoids are synthesized in small quantities, it is necessary to bioassay them for their potential efficacy in long-term animal studies. This new project is an essential component of the retinoids program. The system has been employed for retinoid bioassay in a total set of over 24,000 hamster tracheas. Since the tracheal organ culture assay measures the ability of retinoids to control epithelial cell differentiation, it may predict the effectiveness of a new retinoid for prevention of epithelial cancer. Obviously, any in vitro test has dangerous liabilities for prediction of in vivo activity; in spite of these limitations, the tracheal organ culture assay is a most valuable procedure for initial evaluation of the biological activity of a new retinoid. It is extremely sensitive and is used routinely to evaluate activity of new retinoids, the concentration of which may be as low as 10^{-9} to 10^{-10} molar during the assay procedure. Thus, it is possible to measure biological activity with less than a milligram of a new retinoid; with radioactivity labeled retinoid metabolites, assays have been performed with only a few micrograms of material. The assay is relatively brief; test results may be evaluated within a month after it is begun.

The magnitude of this bioassay effort, the need for program continuity, and the national dimensions of the Chemoprevention Program make a separate project devoted exclusively to these studies a necessity within the framework of this highly articulated program.

Chemoprevention of epithelial cancer by retinoids—Proposed first year award, $620,000, four years.

Four studies in the Chemoprevention Program are investigating the efficacy of retinoids for inhibition of epithelial cancer in well defined animal models. These long term studies investigate the inhibition of N-nitroso-N-methylurea (NMU)-induced mammary cancer; 1,2-dimethyl-hydrazine or NMU-induced

colon cancer; N-butyl-N-(4-hydroxybutyl) nitrosamine-induced bladder cancer, and N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide (FANFT)-induced bladder cancer. The proposed effort concerns long term development of more potent, less toxic, organ-specific retinoids for chemoprevention, and the definition of strategies for their optimal use.

Nutritional and other in vitro requirements of cultured human epithelial cells—Proposed first year award, $1 million, three years.

The Chemical/Physical Carcinogenesis Branch proposes to support studies to determine optimum conditions for the in vitro culture of epithelial cells derived from norman human organs that are at high risk for cancer. These studies, in concert with other data, will advance understanding of interspecies differences in carcinogenesis and make the extrapolation of data of animals to humans more valid.

Currently available tissue culture systems were developed for chick embryo fibroblasts, mouse "L" cells, malignant cervical epithelial cells (HeLa), and primary monkey epithelial cells. Optimum culture conditions for the foregoing may be quite different than those required for the culture of normal human epithelial cells. The proposed effort would encompass: (a) development of well defined nutritional and other environmental conditions for growth of human epithelial cells; (b) development of new methods and the application of existing methods to characterize cells as normal, epithelial, and organ-specific; and (c) isolation and characterization of epithelial cell lines capable of a useful number of population doublings in vitro. These epithelial cells would be made available to the scientific community. The ultimate goal would be to achieve multiplication of normal, diploid, epithelial cells in media that contain only defined, low molecular weight nutrients and small amounts of highly purified macromolecular regulatory factors.

Woodchuck hepatoma model—Proposed first year award, $250,000, five years.

Studies in Asia, Africa, and the Pacific and Mediterranean areas have demonstrated an excess of markers of hepatitis B virus (HBV) infection in patients with primary hepatocellular carcinoma (PHC) compared with matched controls or with the general population. Although this phenomenon has several possible interpretations, it is possible that HBV acts either as a carcinogen or as a cocarcinogen in persistently infected hepatocytes. If persistent HBV infection is a significant oncogenic factor in hepatocellular carcinoma, prevention of HBV infection in childhood should reduce the incidence of PHC. The development of an effective vaccine against HBV is well under way and the National Institute of Allergy & Infectious Diseases is currently supporting immunogenicity and efficacy trials of several vaccine preparations. However, trials to measure the impact of immunization on PHC are years away, if indeed they can be satisfactorily conducted at all.

Recently, the eastern woodchuck (Marmota monax) was reported to harbor a virus morphologically similar to human HBV. In addition, a large percentage of animals trapped or killed in the wild had hepatocellular carcinoma. Since the woodchuck seemed to be an excellent model for human HBV, the NIAID established a small colony of 32 woodchucks at Poolsville using wild animals trapped in early fall of 1978. These animals, plus 19 others, were included in studies conducted by Georgetown Univ. under contract to the NIAID. Fourteen of the 51 animals were positive for viruslike particles that possessed endogenous DNA polymeras (a marker associated with hepatitis B virus). Furthermore, the particles were morphologically similar to HBV. There was also some degree of cross-reactivity between the woodchuck virus and the HBV surface antigen antibody system of man. Two of 32 woodchucks of the NIAID colony, both carriers of the woodchuck virus, were positive by human AFP assay and had gross liver tumors.

The woodchuck virus and HBV appear to represent a novel class of DNA viruses. Although the data are limited, there are striking similarities between the two viruses and the infections they produce. Early exposure leading to chronic infection and PHC, with or without cirrhosis, has been postulated in man but proof of this process will be difficult to obtain. A woodchuck model utilizing colony-born animals offers an opportunity to evaluate this process under controlled conditions and over a much shorter (four year) time span. Additional experimental approaches utilizing this model would include maternal transmission, mechanisms of persistent infection, and effects of active immunization.

The development of the woodchuck model will require colony-born animals to ensure quality and known serologic negative status. In addition, a facility will be required for housing animals on experiment and sufficient staff for performing bleedings, biopsies, inoculations, etc.

Dose response studies on phenolic antioxidants—Proposed first year award, $400,000, four years.

Strategies for cancer prevention involving reduction or elimination of the population's exposure to environmental carcinogens may not always be possible. The experimental approach to the chemoprevention of cancer therefore seeks to take advantage of the findings that certain chemical compounds inhibit the tumorigenic effects of chemical carcinogens. A large number of studies in experimental animals has demonstrated the feasibility of this approach.

The relatively new area of chemoprevention requires the acquisition of basic knowledge, among which is dose/response information on individual chemoprevention agents. The Chemical/Physical Carcinogenesis Branch proposed to initiate studies on dose/response relationships, emphasizing the pheno-

lic antioxidants. Experimentally, these antioxidants have shown inhibitory activity against many classes of carcinogens and against tumors at many different organ sites. However, in almost all reported studies, very high levels of these compounds have been employed. Since they are consumed by man at much lower levels, the Branch wishes to determine their efficacy at lower doses and against lower doses of carcinogen.

Normalization of the malignant phenotype—Proposed first year award, $500,000, three years.

This project involves the suppression or reversal of malignancy by means other than cell destruction. There are examples in the biomedical literature of the spontaneous or induced modulation of the neoplastic properties of tumor cells in various experimental and clinical situations. These cells subsequently approximate normal behavior. Further, the diseases associated with them may no longer progress and, in some instances, are eliminated. Several workshops have considered such phenomena. One conclusion of the workshop on "Suppression of the Malignant Phenotype" was the desirability of initiating a systematic search for substances that "induce differentiation or otherwise significantly modify the malignant phenotype." The proposed effort will involve the search for natural and/or synthetic substances that modify the cancerous properties of malignant cells and will identify those that are effective in reducing or eliminating experimental malignant disease.

Naturally-occurring and/or synthetic substances will be sought which (1) normalize the phenotype of virus-transformed cells in vitro according to selected criteria in well characterized virus-cell systems; (2) substantially reduce or eliminate the oncogenicity of viable cells; and (3) are effective in safely reducing or eliminating the associated natural or induced malignant disease.

While there are encouraging studies of specific substances, both natural and synthetic, that have been found to suppress or reverse the malignant phenotype (e.g., retinoids), to our knowledge there is no concerted effort to screen for this activity for the purpose of discovering novel structures of therapeutic potential.

Virus transformation systems are the most advantageous models for this endeavor. Not only are viruses powerful transforming agents, but they provide techniques and markers which allow investigators to follow the intricacies of the process of neoplastic transformation. The discovery of agents which suppress or reverse the process is bound to stimulate research on mechanisms. For this purpose, virus transformation systems would be ideal.

The Board approved a proposal for a five year study to undertake identification of natural carcinogenic products in foods, with an estimated first year cost of $750,000. DCCP staff had submitted it as a contract supported program, but Board members objected.

"This raises the question of whether the contract mechanism is the suitable way to do this," commented Board member Bernard Weinstein. "What's missing are areas, novel approaches. People have been working in this area without much progress. . . . I would like to suggest that we approve this as an important area, and ask staff to come back with more specific proposals."

The Board recommendation was that if the project is initiated, it should be grant supported, and DCCP Director Gregory O'Conor agreed. Proposals would be solicited through a request for applications, and the $750,000 would be earmarked for the program.

The staff's justification for the program:

Natural carcinogens occur as constituents of plants or as metabolites of microorganisms. Inadvertently ingested, they may initiate an irreversible process which may lead to cancer, although they may not produce immediately recognizable ill effects. Since several thousand species of plants, fungi, and microorganisms are known, it is impossible to test for potential carcinogens all the materials in which they are consumed. Some clues are therefore needed to select those that warrant priority for investigation. The Special Programs Branch wants to initiate a comprehensive program for identifying carcinogenic natural products to which animals and humans are exposed in their diet. The first phase of this project would involve epidemiologic studies on populations exposed to potentially carcinogenic foods. These populations will be in Africa, South America, Asia, Turkey, Scotland, and elsewhere. The second phase of the project would involve attempts to isolate, identify, and test suspected carcinogens in foods identified as carcinogenic in the epidemiologic studies.

The recompetitions for information resource projects include the contract with SRI to provide information required by the Chemical Selection Working Group and to perform special studies on structure activity relevant to chemical carcinogenesis. "The resource is essential to the decision making process at all levels of NCI where questions arise as to source of chemicals, production use, exposure to man, biological properties, and summaries on epidemiological and animal studies," the staff justification said.

The project includes other functions such as updating and expanding old and new categories of human exposure classes—soaps and detergents, cosmetics, prescription drugs, water pollutants, air pollutants, pesticide class, etc.

Estimated funding for the first year of the new contract, FY 1981, is just under $1 million.

Another of the recompetitions is the basic ordering agreement with a consortium of eight organizations, with an estimated total cost of $300,000 in the first year. The contractors identify, classify and quantify those contaminants that are carcinogenic and mutagenic which appear in the various environmental media.

The other two recompetitions are contracts with the International Agency for Cancer Research. One, with 1981 funding estimated at $450,000, is for collection and evaluation of existing data on carcinogenic risk of chemicals to man and for publication of survey on chemicals being tested for carcinogenicity. The second, estimated at $300,000 for 1981, for a survey of compounds which have been tested for carcinogenicity.

In a recent appropriations bill, Congress had directed that NCI devote $15 million to research supporting the mission of the Environmental Protection Agency. EPA has as one of its missions the taking of regulatory action against substances which have been demonstrated to be carcinogenic.

EPA's position at first was that NCI should hand over $15 million, which EPA would use as it saw fit to meet the congressional mandate. NCI demurred and provided a list of studies it was already supporting which were related to EPA's mission (this is in addition to the NCI-EPA interagency agreement, under which projects are jointly carried out by the two agencies).

EPA countered with a proposal for a study of the interspecies relationships of metabolism, pharmacokinetics and toxicities. "The principal hypothesis to be evaluated in this program is that knowledge of the metabolism, pharmacokinetics, repair capabilities and toxicity of a chemical in one mammalian species combined with knowledge of the metabolism and pharmacokinetics of the chemical in a second mammalian species can be used to predict toxicities in the second species," the EPA proposal stated.

The DCT Board agreed that such a project would be worthwhile. But NCI staff first will complete an analysis of projects it is already supporting in the interspecies relationships area. If there are identifiable gaps in the studies and if the ongoing studies do not amount to the $15 million mentioned by Congress, some additional work will be done, probably at Frederick Cancer Research Center.

"I can't disagree with the concept that we should know more about how different species react to carcinogens," said Board member Lloyd Old. "But I wonder if we know enough about the varying reactions of animals in the same species. I don't think there is enough being done with inbred species. I'm not saying interspecies studies are not important, but just that we have a tremendous resource with inbred animals."

"This has much to do with the role of NCI," Weinstein said. "In the past, it has always been the organization to do basic research, and let others take it from there. I'm impressed that when the going gets rough, when they want to understand how to do it, they always come back to NCI."

"As time goes on, what was once basic research becomes more related to actions," said Board Chairman Peter Magee.

"Yes," Weinstein agreed. "We have to keep a pool of money available to do these things. We can't assume that others will do them."

FINAL ISSUE OF THE YEAR

This issue of *The Cancer Letter* is the final one of 1979 and the last in Volume 5. The next issue, Vol. 6 No. 1, will be published Jan. 4, 1980. The office of *The Cancer Letter* will be closed from Dec. 21 through Jan. 1.

Best wishes for the Holidays and the New Year.

MIHICH SUBCOMMITTEE RECOMMENDATIONS FOR DEVELOPMENT OF ANTIGENS LISTED

The final recommendation of the Mihich subcommittee on the Biological Response Modifiers Program dealt with definition of distinctive cell surface antigens of human cancers and development of immunologic antigen preparations (other recommendations appeared in the Nov. 9, 16 and 30 and Dec. 7 issues of ***The Cancer Letter***). The summary of the final recommendation follows:

One biological response of the cancer patient which can possibly be modified to therapeutic advantage is the immune response to cancer-restricted cell surface antigens. There are two basic approaches by which augmentation of the immune response to cancer antigens can be induced, nonspecific immunopotentiation which constitutes the bulk of past and current efforts at cancer immunotherapy, and specific immunization which has not really been evaluated in the treatment of cancer but which has contributed much to the control of infectious diseases.

It is the knowledge of microbial antigens which has permitted the development of successful specific immunization against infections and relegated nonspecific immunostimulants to an adjuvant role. The lack of knowledge of human cancer antigens, on the other hand, has long prevented exploration of specific immunization in the context of cancer as it should be explored, using preparations of defined cancer-restricted antigenicity and demonstrating their immunogenicity in cancer patients.

It is our contention that progress in the definition of human cancer cell surface antigens now permits investigation of specific immunization, and that it should be a component of the Biological Response Modifier Program from the start. The three approaches that can be envisaged are: 1) active immunization with immunogenic preparations of cancer-restricted antigens, 2) "passive" transfer of immunity with specific antibody (the antibody being expected to cause complement-mediated cancer cell destruction) or the use of specific antibody conjugated with cytotoxic drugs or radioisotopes for cancer cell-restricted delivery of these agents, and 3) "adoptive" transfer of immunity with specifically sensitized lymphocytes.

While passive transfer of immunity may become

feasible with hybridoma produced monoclonal antibodies in the near future, more developmental work is required before this approach to therapy is ready for clinical testing. Similarly, adoptive transfer of immunity with lymphocytes may become a realistic possibility as a consequence of the discovery of the T cell growth factor which permits propagation of specifically sensitized T cell clones in vitro. But again, more work in the laboratory is required before this approach can be tested in the clinic. Specific active immunization, on the other hand, can be tested clinically now based on the accomplished definition and classification of cell surface antigens of some human cancers such as malignant melanomas, renal cell cancers and astrocytomas.

By autologous serological typing, three classes of cell surface antigens have been identified. Class 1 antigens are restricted to autologous tumor cells and cannot be detected by absorption tests on normal or malignant cells of any other type, autologous, allogeneic or xenogeneic. Class 2 antigens are found on autologous as well as certain allogeneic tumors, but cannot be detected on normal cells. On the basis of current evidence, Class 1 and Class 2 antigens can be considered tumor-restricted antigens capable of antigens capable of eliciting humoral immunity in the autologous host.

In contrast, Class 3 antigens are a diverse and complex group, with some antigens showing differentiation characteristics, some allo-antigenic characteristics, and some heterospecific characteristics. Based on the definition and classification of cancer cell surface antigens now accomplished, we propose that, from the first year, the BRM program support the construction and clinical testing of various types of cancer antigen preparations with the long term objective of developing maximally immunogenic preparations from types of cancer whose cell surface antigens have been defined serologically.

Even under the most appropriate circumstances and with a most carefully designed study, the testing of human cancer antigen preparations is fraught with difficulties and uncertainties ranging from appropriate type, dose and route to suitable patient selection (type and stage of cancer), to a critical evaluation of clinical response (tumor reduction, tumor recurrence, survival time).

Given this array of variables, a sequential analysis of the clinical effectiveness of different preparations in various patient populations would be, by evaluating clinical response alone, extremely time consuming and expensive and possibly not result in any clearer a picture as to the value of this approach than has emerged from past studies. What is required for the development of immunogenic cancer antigen preparations are methods to assess effectiveness that are both rapid and objective and that can be used to guide the step by step process of vaccine construction and testing.

With regard to vaccines against infectious diseases, serological responses to bacterial or viral antigens have been an essential step in their development. The lack of comparable serological tests to monitor the effectiveness of cancer vaccines in humans has been a major impediment to investigating this approach to cancer therapy. With the development of autologous and allogeneic typing systems for defining cell surface antigens of melanoma and other cancers, we now have serological tests of requisite sensitivity and specificity that can be used to gauge the immunogenicity of cancer vaccines. With these methods, we recommend to test in a sequential fashion the immunogenicity of different cancer antigen preparations in series of 10-15 patients each. Examples of preparations to be investigated are:

1. Irradiated cultured autologous cancer cells—to permit immunization with Class 1 antigens restricted to the autologous cancer.
2. Irradiated cultured allogeneic cancer cells suppressing cross-reacting Class 2 antigens—to exploit the possibility that foreign determinants present on the allogeneic cell surface may facilitate or "help" immune recognition of tumor-restricted antigens.
3. Irradiated cultured autologous or allogeneic cancer cells infected with nonpathogenic viruses (e.g., vesicular stomatitis virus, vaccinia virus)—based on the evidence that preparations of virus-infected tumor cells are more effective immunogens than comparable preparations of noninfected tumor cells.
4. Irradiated chemically modified autologous or allogeneic cancer cells—to explore means of coupling "helper" determinants to the cell surface (e.g., PPD coupled to cancer cells via Con A for immunization of BCG-sensitized individuals).
5. Irradiated Class 1/2 antigens formed by fusing autologous cancer cells with (a) allogeneic cancer cells, (b) allogeneic B cell lines or (c) xenogeneic cells—to induce foreign helper determinants.
6. Immunogeneic forms of isolated Class 1/2 cancer antigens.

Support should be restricted to programs which promise evaluation of changes of the patients' immune response to defined cancer-restricted antigens, induced by administration of these preparations.

NCI CONTRACT AWARDS

Title: In vivo screening program
Contractor: EG&G Mason Research Institute, $7,350,543.
Title: Correspondence course on lung cancer and asbestos-related pulmonary disease
Contractor: American College of Chest Physicians, $115,352.

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-CM-07336

Title: *Adjuvant trials in resectable and partially resectable non-oat cell lung cancer and pathology reference laboratory to support the clinical trials*
Deadline: *Feb. 5*

NCI requires organizations having capabilities and facilities to continue current studies of the Lung Cancer Study Group on patients with non-small cell lung cancer. Studies will focus on early stages of surgically resectable disease in an attempt to determine the efficacy of additional therapeutic modalities in prolongation of survival. Additionally, the treatment of partially resectable locally advanced non-small cell lung cancer will be evaluated.

To be considered for a clinical award, each offeror must demonstrate its ability to enter 50 new cases of non-oat cell lung cancer on study per year. A minimum of 25 of these patients shall have stage 1 or stage 2 disease as defined by the World Health Organization TNM Classification. It is anticipated that multiple awards will be made for this clinical trial. In addition to the clinical trial, separate proposals are solicited for the operation of a pathology reference center to support the above mentioned clinical trials. The clinical contractors will send all pathological specimens to the pathology reference center for standardization of criteria of histopathological cell type.

Offerors may submit proposals for either the clinical trials or pathology reference center or both. There will be separate review of clinical trial proposals and those for the pathology reference center.

RFP NCI-CM-07339

Title: *Therapy of patients with gastric and pancreatic carcinoma*
Deadline: *Feb. 5*

NCI requires organizations to conduct multimodal studies on patients with pancreatic or gastric carcinoma. These five year contracts will continue the work of the Gastrointestinal Tumor Study Group (GITSG). The GITSG is engaged in the development and validation of therapies of gastric and pancreatic cancer in various stages of disease, including minimal residual, locally unresectable and advanced disease.

The main objective of each contractor will be the accrual of patients into group protocols. These standard protocols will be developed by the group members and the government project officer. Successful offerors may also participate in pilot studies that may lead to group protocols. Additionally, successful offerors shall participate in the scientific analysis of terminated studies and the formulation of subsequent trials.

To be considered for award each offeror must demonstrate ability to enter 50 patients with gastric cancer and pancreatic cancer per year on controlled studies. Out of the required 50 patients per year, at least 20 patients must have each tumor type. It is anticipated that multiple awards will be made to meet the NCI's patient accrual requirements.

Contract Specialist for above two RFPs: Charles Lerner, Cancer Treatment, 301-427-8737

RFP NCI-CM-07348-26

Title: *Therapy of patients with brain tumors*
Deadline: *March 3*

By means of a group of clinical resources contracts NCI desires to continue its studies of intensive multidisciplinary therapy of patients with malignant gliomas and other types of intracranial tumors, and to determine the efficacy of a number of therapeutic approaches. Data obtained during the course of these studies will provide information on treatment efficacy, possible intrarelationships between tumor morphology, extent and clinical stage of the disease, changes in roentgenographic finds, alterations in nuclear imaging, and pharmacotoxicology of selected agents.

Each contractor must represent a single institution in reasonable geographical continuity and possess a systematized research facility and sophisticated operational task force with demonstrated capability of conducting multitherapy phase 2 and 3 clinical studies. A meaningful coordinated commitment shall exist between the neurosurgical department and the neuropathology and radiation therapy departments of each institution, as well as an effective working relationship between the aforementioned groups and the neurology, oncology, hematology and clinical chemistry departments.

Since several institutions are expected to be selected for these studies, each institution must be willing to collaborate with the NCI project officer and staff, and the members (other contractors) of the Brain Tumor Study Group (BTSG) in the conduct of ongoing clinical trials. A minimum of 35 evaluable patients, having a microscopically confirmed diagnosis of malignant glioma, shall be required each year. A minimum of 20 newly operated (first craniotomy) patients shall be accrued each year to the phase 3 studies and the balance of the accrual requirement with patients with recurrent gliomas into phase 2 studies.

Each contractor shall have the overall logistical mobility for conforming to the protocol requirements. In addition, the neuropathology department of one of the selected contractors may be selected to function as the neuropathology coordinating center for the group.

It is anticipated that multiple awards will be made as a result of this RFP and that incrementally funded contracts will be awarded for a period of five years. This RFP represents a recompetition of the program, "Therapy of Patients with Brain Tumors."

RFP NCI-CM-07337-26

Title: *New drug development clinical trials in solid tumors*

Deadline: *Feb. 5*

Conduct phase 2 and 3 studies in patients with disseminated solid tumors such as: cancers of the lung, breast, prostate, bladder, kidney, testicle, overy, endometrium, cervix, head and neck, stomach, pancreas and colon, as well as lymphomas, melanomas and bone and soft tissue sarcomas. In particular, NCI wishes to have substantial input in the design of studies which shall insure the accurate and efficient evaluation of new drugs and other therapies in these selected tumors. This input will include specific program-directed research from qualified institutions as well as direction and approval of investigator-instigated projects.

A minimum number of 200 patients will be required, with minimum requirements for each tumor type dictated by the particular protocols which are approved for each institution. It is anticipated that multiple awards will be made as a result of this RFP and that incrementally funded contracts will be awarded for a period of five years. This RFP represents a recompetition of the program, "Phase 2 and 3 Studies in Patients with Disseminated Solid Tumors."

Contract Specialist for the above two RFPs: Carolyn Swift
Cancer Treatment
301-427-8737

RFP NCI-CM-07326

Title: *Preparation and purification of viral components*

Deadline: *Jan. 30*

The Developmental Therapeutics Program, Div. of Cancer Treatment, is seeking a contractor for the procurement of large quantities (40-50 liters per week) of feline and primate type C viruses. These viruses should be grown in cell lines free from mycoplasma. The primate viruses should be propagated when possible on primate cell lines. The purified and concentrated viruses will be used by the government for preparation of viral antigens including the reverse transcriptase, high molecular weight RNA and cDNA.

It is important that the contractor be able to supply fresh concentrated virus on wet ice within one hour after harvesting. Hence, it is requested that the offerors for this contract should be within one hour driving distance of NIH Bethesda location. It is anticipated that one award will be made for a three year period.

Contract Specialist: Otis Parham
Cancer Treatment
301-427-8737

RFP N01-CP-05611-72

Title: *Survey of compounds which have been tested for carcinogenicity—supplements for 1974, 1975, 1976, 1977, 1978, 1979 and 1980*

Deadline: *Feb. 28*

NCI is interested in having published a supplement of PHS Publication 149 presently entitled "Compounds Which Have Been Tested for Carcinogenic Activity." The contractor must have access to medical and technical library collections which provide adequate and balanced coverage of the scientific literature pertaining to studies of the effects of chemical substances in animals.

It is expected that approximately 650 journals will be searched. However, the offeror is requested to submit a list of those which would be considered as primary journals relevant to this search. In addition, the search will be augmented by use of computer resources such as ICRDB, Toxline, Cancerline, etc. The journal search shall cover literature for the calendar years 1974, 1975, 1976, 1977, 1978, 1979 and 1980.

The contractor will exhaustively search this scientific literature for documentation of tests which will be selected according to specific guidelines: 1) search the scientific literature (including journal articles, reports, monographs, and books) selecting appropriate documents and review these documents for pertinency; 2) extract specific data from these documents and index the documents with respect to selected items of the extracted data. This material will be presented as manuscript copy conforming to size and quality specifications of the Government Printing Office. A copy must be presented to NCI of each article and report from which data is extracted; and 3) generate a computer-readable tape of the indices with record format to be specified by the project officer.

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