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NCI TO BROADEN SUPPORT, ESPECIALLY FOR STAFF, THROUGH CORE GRANTS TO COMPREHENSIVE CENTERS

New guidelines being developed by NCI for determining admissible items eligible for core grant support at comprehensive cancer centers will broaden that support, particularly for the newly emerging centers.

Simeon Cantril, who heads NCI's centers program, brought a draft of the new guidelines to the meeting this week of the National Cancer Advisory Board Subcommittee on Centers. Cantril said the guidelines would be incorporated into a new edition of the booklet NCI published several years ago which describes the characteristics applicable to comprehensive cancer centers. The new edition should be available in January, Cantril said.

The draft guidelines listed nine categories under admissible items and costs which could be paid out of center support (core) grants. Subcommittee Chairman Denman Hammond and other committee members emphasized in discussing the guidelines that the key word was "admissible"—that is, "you don't automatically get one helping of everything," Hammond said. "You have to state your case," in the grant application and at the time of the site visit. Requests would have to survive the peer review process.

(Continued to page 2)

In Brief

CANCER CONTROL NEEDS MORE ONCOLOGISTS, DCT RECRUITING FOR PRESTIGIOUS COMBINED JOB

MORE JOB openings at NCI: The Div. of Cancer Control & Rehabilitation needs several more oncologists, in any of the disciplines. They'll go in either in the "expert consultant" category or GS 15 or higher, at $30-37,500. Call or write DCCR Director Diane Fink, 301-427-7996, Blair Bldg., 8300 Colesville Rd., Silver Spring, Md. 20910. Vincent DeVita, director of the Div. of Cancer Treatment, is still looking for someone to fill the prestigious combined role as associate director for clinical oncology and clinical director. . . . **CORRECTION:** In publishing recently abstracts from the VIIth International Symposium on Comparative Research on Leukemia and Related Diseases, ***The Cancer Letter*** implied copies of the proceedings would be available at no charge. Actually, the 600-page volume will have to be purchased, when published by Karger in mid-1976. Information concerning publication may be obtained by writing to David Yohn, IACRLRD Secretary General, Ohio State Univ., 1580 Cannon Dr., Suite 357, Columbus, Ohio 43210. . . . **HAZLETON LABS** has opened a Japanese liaison office in Tokyo, with C.K. Moriya as general manager. . . . **COOPERATIVE GROUP** chairmen, DCCR staff will meet Nov. 24 at the Blair Bldg. to discuss mutual problems, coordination of programs that are cropping up side by side in many hospitals. The meeting is open, starting at 9:30 a.m.

NEW GUIDELINES FOR CORE GRANT SUPPORT WILL BE MORE FLEXIBLE

(Continued from page 1)

The nine categories are:

* **Professional personnel.** Senior leadership personnel—center director, associate directors for each research or programmatic area. Major program directors and policy advisors—scientists responsible for major program areas or program projects. In general these individuals will be senior scientists, quite often with major reputations. Staff investigators—personnel who conduct or are in charge of independent cancer related projects which have received external peer review and funding prior to the cancer center support grant (CCSG) application. The project should be clearly relevant to the objectives of the National Cancer Plan. A significant portion of the individual's time should be allocated to implementing the activities.

* **Administration.** Staff necessary for the central administrative and fiscal aspects of the operation and coordination of activities at the center. Included are such functions as grants and fiscal management; business and personnel management; preparation of budget; administration of hospital costs; and the appropriate secretarial support. It is not intended that these direct costs replace indirect costs, which are included in the institution's indirect cost rate. Also includes domestic travel costs associated with general development and operation of the center, particularly local travel required by the center's outreach efforts. Foreign travel is allowed only with prior NCI approval.

* **Planning and evaluation.** Includes costs for such outside consultant services associated with these activities such as a scientific advisory committee, ad hoc scientific and technical consultants or consulting firms providing needed experience and technical assistance necessary for the center as a whole. Costs for planning new center activities are allowed. Costs for the overall evaluation of the program of the center over a period of time is encouraged and allowed.

* **Shared resources and services.** Includes facilities, equipment and services available to many members of the center. Such resources should be those which require long-term stable funding not possible by utilization of an individual research project. Library activities are allowed if justified carefully.

* **Developmental funds.** Program development funds should allow the center director flexibility in developing new programs or strengthening existing programs to correct weaknesses. These funds will be limited to three years, and the grant application should describe how future funding will be obtained. Research development funds are designed to allow the center director flexibility in developing innovative ideas that arise during the tenure of the grant. These funds should not be used to substitute for regular project grants and would be limited to no more than two years.

* **Alteration and renovation.** Alteration and renovation of an existing structure may be paid for by the support grant. The present policy of NCI is that up to 100% of the costs of alteration and renovation may be paid by a CCSG, provided such costs are less than $75,000 or 25% of total direct costs (excluding patient care costs), whichever is less, for three years of the total project period. For amounts over this figure, application may be made for a grant under NCI construction program. For grants under the aegis of the construction program the rate of cost participation by NCI will be up to 75% of the eligible costs of an approved project. At least 25% of the costs must be provided by the grantee from nonfederal sources. It should be noted that any space vacated by personnel moving to space altered or renovated with NCI funds should become cancer center space under the control of the center director. As an alternative, the institution, in concurrence with the center director, may make comparable space available for reasons proposed by the institution which are acceptable to NCI.

* **Equipment.** This category includes items of major equipment that can be shown to be needed for shared services for multiple projects or investigators within the cancer center.

* **Supplies.** Consumable supplies, such as office materials, chemicals, glassware, and similar items may be funded by a CCSG for purposes associated with the centralized functions, with the inauguration of new programs, and with the limited augmentation of established high priority programs.

* **Policies, assurances and certification.** All policies (including all necessary assurances and certification) which are applicable to research projects as outlined in the NIH Policy Statement (72-S) will apply also to CCSG.

NCAB Chairman Jonathan Rhoads objected to broadened provisions for payment of staff salaries. Rhoads said it has been NCAB's position that core support should be limited to the senior leadership—center director and associate directors, "certainly not for the staff investigators." Salaries of scientists directing or involved with research projects should be paid out of those individual project grants, Rhoads contended.

"This could reopen the charge that things get by in center grants that wouldn't in the regular peer review process," Rhoads said. "I'm sure that in some circumstances we might want to support some of those people (through core grants), for short terms. But unless the Board has changed its mind, I don't think it would support this category as it is."

Lee Clark, member of the President's Cancer Panel, commented that a center "that couldn't support its senior personnel (through other than core grants or other sources) shouldn't be considered a compre-

hensive center." But Clark acknowledged that core grant support should be flexible in picking up key salaries, particularly in the early stages of the center's development.

Cantril argued, "I feel strongly that this category (support of staff investigators) is very important to assure development of a strong, stable staff." He said NCI's staff reviewers would see to it that applications asking for such support would be properly peer reviewed.

NCAB member Gerald Murphy offered four suggestions for inclusion under the shared resources and services categories—support for shared services that could achieve cost-saving economies of scale unattainable at the scale of individual project reimbursement; central projects that would stimulate multidisciplinary interaction and cohesion in the scientific program of the center; support for vital services where necessary to assure continuous opportunity to deliver a service irregardless of fluctuations in current utilization; and the need for centers to document the allocation of matching funds that demonstrate the internal resource commitment of the center to the project.

"I mean really document them" Murphy said. "I can't state that too strongly, especially the need to demonstrate the internal resource commitment."

Cantril said Murphy's suggestions would be incorporated into the guidelines.

CARCINOGENESIS SUBCOMMITTEE WRITES DRAFT FOR APPLICATION TO CHEMICALS

As pressures build for action by the federal government to remove carcinogenic substances from the environment, the regulatory agencies are turning to NCI with increasing frequency for advice and support in determining which substances are dangerous and should be removed or controlled (*The Cancer Letter*, Nov. 14).

NCI Director Frank Rauscher asked the National Cancer Advisory Board Subcommittee on Environmental Carcinogenesis to develop a definition or some criteria to use in the determination of chemical carcinogenicity. The subcommittee, chaired by Philippe Shubik, wrote the following draft at its meeting last week. A final draft will be presented at the subcommittee's meeting in January.

CRITERIA FOR ESTABLISHING THE CARCINOGENICITY OF CHEMICALS

A. CRITERIA IN HUMANS

Human carcinogens are specifically defined as those agents, alone or in combination, for which there is adequate evidence that exposure increases the risk of malignant neoplasms in humans to levels higher than in a comparable population not exposed (or exposed at a lower dose) to the same agents.

Some of the acceptable evidence includes: Response directly related to exposure (both duration and dose); incidence and mortality differences between countries; altered incidence in migrant populations; time trends in incidence (including lowering incidence when specific agents are removed from the environment); and prospective studies of the consequences of exposure. Epidemiologic studies can be quite insensitive. Because of this the absence of such evidence does not establish the safety of a suspected material.

B. CRITERIA IN EXPERIMENTAL ANIMALS

In experimental animals, a carcinogen is defined as a substance which when administered to groups of animals results in reproducible increases in incidence of malignant neoplasms in the treated groups when compared to control groups of animals maintained under identical conditions but not given the test compound. The increased incidence of neoplasms in the experimental group must be statistically significant when compared to the control group and the sole experimental variable between the control and the experimental group must be the absence or presence of the single test compound. The demonstration of a dose-dependent relationship provides further confirmation of positive results.

A malignant neoplasm is one composed of a relatively autonomous population of cells displaying progressive growth with invasion and destruction of normal tissues and capable of causing death to the host. Malignant tumors frequently but do not always metastasize.

Benign neoplasms are defined as neoplasms which contain a relatively autonomous hyperplastic population of cells which do not cause extensive invasion of normal tissues and do not metastasize. In particular cases they may, however, endanger the life of the host. It is recognized that the cytologic and histologic criteria for whether a lesion is benign or malignant differ somewhat depending upon the tissue in which the tumor arises. Evaluation of the malignancy of a given lesion should, therefore, follow standard criteria used by experimental oncologists and pathologists, recognizing that in equivocal cases the precise diagnosis may require a panel of experts.

Positive results obtained in certain animal test procedures (see below) do not in themselves constitute definitive evidence for carcinogenicity. Positive results in such procedures do suggest, however, that the compound is potentially carcinogenic and therefore warrants further study. Examples of these test procedures include the following:

1. Assays in which the strain of animals used has a very high (greater than 10%) spontaneous frequency of a particular tumor and the test compound increases the incidence and/or shortens the lag in the appearance of that tumor.

2. Assay systems in which animals receive a known carcinogen, receive other foreign material (in addition to the vehicle for the test compound), or are subjected to modifying factors, in addition to the test compound.

other might be applicable to mammary epithelium and might play a role in "macrophage blocking" or other changes occurring in the microenvironment at the time neoplastic cells lodge in the tissue. Thirdly, because special conditions for communications between mammary neoplastic epithelium and endothelium or fibroblasts of bones, lungs, or liver might account for the organotropism of metastases. Human mammary neoplastic cells are available and a method for collecting and cultivating human endothelium has been described. The BCTF already has an RFP concerned with osteotropism of metastases. Biologists involved in cell communication studies may have submitted proposals. If not, an attempt to involve cell communication biologists in the study of mammary cancer metastases should be seriously considered.

The syllabus included descriptions of three other research areas, including existing contracts and grants, but for which Gullino offered no suggestions for new work. They were:

Isolation, cultivation and recognition of normal and neoplastic mammary cells of epithelial origin.

Genetic, environmental, dietetic and other factors in breast carcinogenesis.

Diagnostic tools in breast cancer detection.

The reorganization includes a BCTF Steering Committee, headed by Gullino and consisting entirely of NCI staff members. Chairmen of the committees are:

William Taylor, Mayo, Diagnosis; Anthony Miller, National Cancer Institute of Canada, Epidemiology; Yale Topper, National Institute of Arthritis, Metabolism and Digestive Diseases, Experimental Biology; and William McGuire, Univ. of Texas, Treatment.

The new meeting schedule, which some members felt might be too ambitious, calls for the committees to meet once every two months. The first day will be in joint session to listen to 10-12 presentations of ongoing work, the second day committees will meet separately for specialized business.

"The joint meeting is necessary to keep everybody informed of the whole program, and the need for six yearly meetings is dictated by the size of the program," Gullino said. "Today the program is too vast and cannot be reviewed in one meeting a year," as was previous custom of BCTF.

BCTF TO HEAR 10-12 PROGRESS REPORTS AT EACH MEETING; SUMMARIES PRESENTED

Among the changes in Breast Cancer Task Force procedure initiated by Gullino will be regular reports from investigators describing progress and problems they are encountering. Gullino said there would be 10-12 of these reports at each of the six general meetings he plans to hold each year.

Summaries of reports presented at last week's meeting follow:

Investigations of Plasma Membranes of Mammary Glands — *Kermit Carraway, Oklahoma State Univ.*

Preparation of purified plasma membranes of mammary tissue is complicated by the difficulties involved in homogenizing the tissue. Partially purified plasma membranes can be prepared by discontinuous gradient centrifugation of a microsomal fraction prepared after homogenization in a Sorvall Omni-mixer. The presence of substantial galactosyltransferase activity suggests that this membrane fraction contains Golgi as well as plama membrane fragments. Treatment of the fraction with digitonin causes a shift in the density of part of the material. The new band has additional enhancements in the 5'-nucleotidase and ATPase specific activities, but essentially no galactosyltransferase. Further characterization of this material is in progress.

Investigations have been performed on the 5'-nucleotidase and Mg^{++} - ATPase of partially purified membranes. At least two forms of nucleotidase (low Km and high Km) are present. Both forms are inhibited by the plant lectin Conconavalin A in a process that shows substantial cooperativity. With the mammary membranes both Km and Vmax are altered by the lectin. Mg^{++}-ATPase is activated by Con A in a cooperative process. In membranes from the 13762 mammary adenocarcinoma only Km is affected by the lectin. The study of plasma membrane enzymes and their perturbation by lectins would appear to offer promise for understanding the role of these enzymes, their association with the membrane and alterations of membrane structure in pathological states.

Metastasis of Mammary Tumors in Perspective — *Untae Kim, Roswell Park*

Immunological and biochemical studies indicated that the spontaneously metastasizing mammary tumor cells shed their surface antigens into the systemic circulation, and seemed to be capable of eluding the host immune surveillance mechanism, while the antigens of nonmetastasizing tumor cells were firmly bound to their plasma membranes. It was also found that the metastasizing capacity of tumor cells was inversely related to the levels of plasma membrane-associated enzymes including cAMP phosphodiesterase. Utilizing these experimental mammary tumor models, the biochemical mechanism of spontaneous antigen-shedding property and the influence of free tumor cell surface antigens on the host immune responses are being studied.

Analyses of glycoprotein turnover in the plasma membranes of mammary tumors indicated that the galactosyltransferase activity was 3-5 times higher in the metastasizing tumors than in the non-metastasizing ones. Furthermore, the number of galactose acceptor sites in the plasma membranes increased with the metastasizing capacity indicating the presence of greater numbers of incomplete glycopeptides on these shedding tumor cell surfaces. Interestingly enough, glycosyltransferase activities including galactosyltransferase, sialyltransferase and fucosyltransferase, in the sera of metastasizing tumor hosts were also markedly elevated as reported by others in cancer patients and tumor bearing animals.

The in vitro lymphocyte migration inhibition (MIF) technique applied to the peripheral lymphocytes, spleen cells and thymocytes from tumor hosts indicated that the migration of lymphocytes from nonmetastasizing tumor hosts was stimulated as compared to normal lymphocytes before an in vitro exposure to their own tumor antigen but it was inhibited after the exposure. On the other hand, the migration of lymphocytes from metastasizing tumor hosts was initially inhibited prior to an incubation with their own tumor antigen but was stimulated after the exposure. The in vitro blastogenesis of lymphocytes from metastasizing tumor hosts, to PHA and Concanavalin A was often irreversibly suppressed, while with the nonmetastasizing, immunogenic tumor hosts the suppressed blastogenic capacity of lymphocytes was not only reversible but often stimulated after surgical excision of the tumor. In the sera of nonmetastasizing tumor hosts, there were tumor specific antibody as demonstrated by the Ouchterlongy immunodiffusion technique, while no tumor specific antibody was found in the sera of metastasizing tumor hosts.

New Probes of Altered Membrane Structure in Malignant Mammary Cells — *Grant Fairbanks, Worcester Foundation*

This project is concerned with the development and exploitation of new technologies for plasma membrane isolation and characterization.

The radiosynthesis of a novel cleavable protein cross-linking reagent, [^{35}S] dithiobis(succinimidyl propionate)("[^{35}S] DTSP"), has been achieved. Because DTSP combines extremely high reactivity with long solution half-life, the radiolabeled cross-linker is a uniquely valuable

FDA'S CONTROVERSIAL CLINICAL TEST GUIDELINES FOR ONCOLOGIC DRUGS

The Food & Drug Administration has written a set of guidelines for investigators to follow in clinical tests of anticancer drugs. Portions of the guidelines have been criticized by NCI executives and advisory group members. FDA does not plan to publish the final guidelines before next spring; in the meantime, persons wishing to offer suggestions or objections may do so by sending them to FDA, Bureau of Drugs, 5600 Fishers Ln., Rockville, Md. 20852.

The guidelines are lengthy, with detailed steps listed for phase I, II, III, IV, and pediatric studies. The preamble to the guidelines appears below; complete text of the rest of the proposal will be published in subsequent issues of ***The Cancer Letter.***

PROPOSED CLINICAL GUIDELINES FOR INVESTIGATIONAL ANTINEOPLASTIC DRUGS

"General Considerations for the Clinical Evaluation of Drugs" contains suggestions that are applicable to most investigational new drug studies, and should be reviewed prior to reading these guidelines. These guidelines, for antineoplastic drugs, are provided to help an investigator formulate his plan of development of a particular substance in conformance with established FDA regulations. They should be construed as general directions, not a set of specific instructions. For this drug class, for instance, it is sometime more efficient to combine Phase I and Phase II (conceptual entities) studies in a single experimental subject. In such cases, the investigator must be sure that his protocol reflects the fact that his experiment is so designed that all of the objectives of both phases can be attained. FDA has a specific mandate to protect all persons receiving drugs in the USA, and a continuing obligation to improve the public's health. This administration seeks to do this by promoting and fostering productive, innovative biomedical research, and preventing dangerous or unproductive clinical research. These guidelines represent one aspect of its efforts.

As most chemotherapeutic agents act by altering cellular metabolism and/or inhibiting cellular proliferation, pathologic and frequently physiologic, the risk versus potential benefit to the experimental subject must be carefully considered before clinical experiments may begin. Many antineoplastic drugs also have oncogenic, teratogenic and mutagenic properties which should be defined preclinically, and assiduously sought for in the clinic. For these reasons cytotoxic compounds are usually not tested in normal subjects.

Because antineoplastic agents as a class have a low therapeutic index, and accepted therapy itself often borders on the "experimental," the treatment of most cancer with drugs should be limited to those physicians who by training and experience are qualified to use the agents. In the often desperate situations of cancer medicine, these drugs in proper hands are of real benefit to appropriate patients. Improperly used, they can be excellent examples of Publius' (1st Century B.C.) observation, "There are some remedies worse than the disease." In this light, it would seem prudent to limit the conduct of phase I and phase II studies to medical oncologists trained as clinical pharmacologists or clinical investigators. Phase II studies on the other hand could be conducted by pediatricians, internists, radiotherapists, and surgeons with a substantial interest in and commitment to clinical oncologic research. All investigators must have ready access to adequate laboratory, and hospital (support) facilities.

Before any clinical trial can begin, those preclinical (animal) pharmacologic and toxicologic studies necessary to prudently begin a trial of the agent in man must be completed, analyzed and prepared for review. As clinical studies progress newly proposed protocols must be shown to be rigorously and soundly based on conclusions derived from prior experience and findings (preclinical and/or clinical). The submitted protocol is the sole basis for its own regulatory judgment. It is assumed that submitted documents (to the FDA) will conform to current standards of scientific writing and reporting, i.e. be clear and concise.

CONTRACT AWARDS

Title: Studies of syngeneic cells, immunological techniques and producing in vitro lymphocytes
Contractor: Weizmann Institute, Israel, $234,713.

Title: CEA and related tumor associated antigens in the diagnosis of cancer
Contractor: New York State Dept. of Health, $61,645.

Title: Measurement of immunological reactivity to human cancer
Contractor: Litton Bionetics, $979,972.

Title: Measurement of aryl hydrocarbon hydroxylase in culture human lymphocytes
Contractor: New York State Dept. of Health, $144,660.

Title: Provide necessary services and support in the conduct of the annual joint working conference of the Virus Cancer Program
Contractor: Courtesy Associates, $32,670.

Title: Conduct immunogenetic analysis of mouse leukemia viruses
Contractor: Fred Hutchinson Cancer Research Center, $272,028.

Title: Continue the maintenance and operation of the Detroit SSMA population based cancer registry
Contractor: Michigan Cancer Foundation, $53,263.

Title: Study of adnenocarcinoma of the prostate
Contractor: Hazleton Laboratories, $86,804.

ABSTRACTS OF PAPERS FROM MEETING OF THERAPEUTIC RADIOLOGISTS

The 17th annual meeting of the American Society of Therapeutic Radiologists was held in San Francisco last month. Selected abstracts of papers presented at the meeting appear below; others were published in the Nov. 7 issue. Copies of complete papers are available. Write to ***The Cancer Letter*** *and include title and authors of papers desired.*

Combined Treatment Modality in Rhabdomyosarcoma in Children – ***A. Razek, C.A. Perez, F. Lee, A. Ragab & T. Vietti, Mallinckrodt Institute of Radiology***

Thirty-nine previously untreated children with rhabdomyosarcoma received radiation therapy at Mallinckrodt. Treatment utilized a coordinated program of surgery, radiation therapy, and combination chemotherapy. The primary tumor was located in the head and neck (24 cases), thorax (2 cases), abdomen (10 cases), and lower extremity (3 cases). Radiation therapy was delivered using supervoltage, high energy photons, and electron beam therapy. The chemotherapy involved Actinomycin-D, Vincristine, and Cyclophosphamide. Twenty of 27 cases (74%) treated from 1968 to 1973 are alive 2-5 years after therapy.

This group of patients will be compared to those treated less radically before 1968. Of the 5 cases with metastatic disease at the time of diagnosis, non survived. No major complications were noted except in cases with orbital rhabdomyosarcoma (3 of 9 cases). A multidisciplinary approach in the treatment of this tumor in children is promising.

Non-esterified Urinary Cholesterol, its Excretion in Women with Ovarian Neoplasms – ***John Frich Jr., Herman Acevedo, Elizabeth Campbell, David Hayeslip & James Gilmore, Allegheny General Hospital***

The urinary excretion of non-esterified cholesterol (NEC) in 56 women with ovarian neoplasms and/or related diseases has been investigated. Twelve patients had non-malignant diseases (cystadenomas, benign cystic teratoma, sclerocystic ovarian disease, fibroma of ovary, hilar cell tumor, leiomyoma and organizing hematoma from pelvis). The malignant neoplasms comprised 35 patients with papillary cystadenocarcinomas; 3 with malignant granulosa cell tumors, 2 with malignant germ cell tumors, 2 with malignant mixed mullerian tumors, and single cases of endometrioid carcinoma and clear cell carcinoma.

The results of our studies showed that all the patients with non-cancerous ovarian lesions showed a normal NEC excretion irrespective of diagnosis, extension or severity of the disease. In contrast, urinary NEC hyperexcretion occurred in patients with the following primary active malignant neoplasms: 18 of 19 cystadenocarcinomas of the serous and/or mucinous types, the single cases of endometrioid carcinoma, the 3 malignant granulosa cell tumors, the 2 patients with mixed malignant germ cell tumors, and one of the 2 patients with mixed malignant mullerian tumor. The single case of clear cell carcinoma had a normal NEC excretion. A normal NEC excretion was also shown by all but 3 patients without any evidence of active disease. In two of these 3 patients, the abnormal results may be explained by an incorrect staging due to lack of omental and peritoneal biopsies. The 95% correlation between the presence of proven active disease and NEC hyperexcretion is notable, considering that cystadenocarcinomas alone constitute more than 75% of all primary malignant neoplasms of the ovary.

CANCER RESEARCH EMPHASIS GRANTS

Title: *In vitro chemical carcinogenesis*

NCI is accepting applications for support of research projects in the area of in vitro carcinogenesis. The objective of this research is to study the interaction of chemical carcinogens and mammalian cells in vitro with particular emphasis on the following problems:

1. The development of new systems for neoplastic transformation in cell culture induced by chemical or physical agents including consideration of the use of human and non-human primate cells.

2. The development and/or refinement of methodology for the early identification and quantitation of neoplastic transformation of cells in culture using new biochemical, cytological or immunological markers (relative to identification of transformation) in established systems.

3. The development and characterization of new approaches for metabolic activation systems for carcinogens and procarcinogens which can be applied to existing in vitro neoplastic transformation systems.

4. The identification or development of biochemical or immunological systems which may serve as early in vitro indicators of transformation processes.

A goal of the in vitro chemical carcinogenesis program is to develop new approaches that can lead to reducing the effect of carcinogenic agents by detecting and identifying chemical carcinogens using in vitro cell systems and by studying their mode of action and possible inhibition.

Since limitations exist with present in vitro methodologies, it is anticipated that the above studies may provide more effective and efficient in vitro systems. It is necessary that continuing efforts be directed toward achieving approaches and methodologies which can define in vitro systems that are more applicable to the basic problems of prevention, inhibition and reversal of carcinogenesis in man.

Nonprofit organizations and institutions, state and local governments and their agencies, authorized federal institutions, and individuals according to NIH grant policies are eligible.

Applicants should propose an individual project. Applicants may elaborate on the purposes, objectives, rationale, and significance stated in this announcement and must complete portions of the applications pertaining to procedural details, the investigator's related experience, facilities, available budgers, and biographical information for key professional personnel. The application should also state the duration of time for which the support is requested. It is anticipated that the project period will not exceed three years and that the level of effort per year should not exceed 2-3 man years in the category of professional personnel.

Use application form NIH-398. In both the covering letter and at the top of the space provided for an abstract on page 2 of the application, identify this CREG announcement by its title and number DCCP 16 and the date of publication as the one to which the application responds. Mail the application and letter to Div. of Research Grants, NIH, Bethesda, Md. 20014. If your institution cannot supply you with form NIH-398, it may be requested from the Div. of Research Grants.

Applications received on or before June 1, 1976, will be processed for study section review in October 1976, and for the National Cancer Advisory Board review in January 1977.

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. Some listings will show the phone number of the Contract Specialist, who will respond to questions about the RFP. Contract Sections for the Cause & Prevention and Biology & Diagnosis Divisions are located at: NCI, Landow Bldg. NIH, Bethesda, Md. 20014; for the Treatment and Control Divisions at NCI, Blair Bldg., 8300 Colesville Rd., Silver Spring, Md. 20910. All requests for copies of RFPs should cite the RFP number. The deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP NCI-CB-64001-31

Title: *Immunotherapy: New approaches to immunotherapy*
Deadline: *Feb. 9*

Proposals are sought for creative approaches in the use of the immune system for cancer therapy. Both animal and human studies are acceptable. Animal work should be relevant to application in man.

RFP NCI-CB-64002-31

Title: *Cancer Immunotherapy: Phase I study of effects of immune stimulants on human immune response*
Deadline: *Feb. 9*

These studies will be aimed at determining maximally tolerated dose and toxicity of immunotherapeutic agents in patients with advanced cancer. In addition, agents will be evaluated for their capacity to restore or to augment immune function.

RFP NCI-CB-64003-31

Title: *Animal models for tumor immunotherapy*
Deadline: *Feb. 9*

These studies will evaluate the parameters of dose, route, schedule of administration, manipulation of tumor cells, etc., in existing successful animal models for tumor immunotherapy. Immunoprophylactic models will not be acceptable.

RFP NCI-CB-64004-31

Title: *Studies of immune stimulants in patients receiving radiation therapy*
Deadline: *Feb. 9*

These studies will document and evaluate the immunosuppression caused by localized radiotherapy and will evaluate the effects of immuno-stimulants on the immune system of such patients. In vitro and in vivo assays for humoral and cellular immune function must be included.

RFP NCI-CB-64005-31

Title: *Immunotherapy using immunoresponsive cells sensitized in vitro by tumor cells, modified tumor cells, or tumor cell fractions*
Deadline: *Feb. 9*

Proposals are sought for animal studies, human laboratory studies, or human clinical studies to evaluate in vitro immunization as a form of immunotherapy against cancer. Sophisticated immunologic techniques including tumor specific reactions are an essential component of this work.

RFP NCI-CB-64006-31

Title: *Evaluation of immunotherapy with tumor preparations in man (active specific immunotherapy)*
Deadline: *Feb. 9*

These studies will evaluate optimum dose, route and schedule of administration of modified or unmodified tumor cells or antigen obtained from such cells to give mamimum immunoresponsiveness to tumor specific antigens in cancer patients. The major thrust of these proposals should be the application of reliable assays to the evaluation of the cellular and humoral tumor specific response to immunization with tumor cells or their products.

RFP NCI-CB-64006-31

Title: *Immunotherapy of squamous cell carcinoma of the lung treated by resection or radiotherapy*
Deadline: *Feb. 9*

The goal of this work will be to evaluate resection or radiotherapy versus resection or radiotherapy plus an immunotherapeutic agent in squamous cell carcinoma of the lung.

RFP NCI-CB-64008-31

Title: *Evaluation of tumor cell "vaccination" in squamous cell carcinoma of the lung*
Deadline: *Feb. 9*

The goal of this work will be to compare results of resection or radiotherapy with the same primary treatment plus tumor cells in addition to the immuno-adjuvant.

RFP NCI-CB-64009-31

Title: *Immunogenicity of "spontaneous" animal tumors*
Deadline: *Jan. 30*

The NCI wishes to support investigations of the immunogenicity of "spontaneous" tumors in syngenic animals. These should be tumors that arise spontaneously in low frequency in inbred animals and are not known to be caused by a viral agent; tumors arising after low exposure to known carcinogens may also be acceptable.

RFP NCI-CB-64019-31

Title: *Clinical evaluation of immunodiagnostic tests for cancer*
Deadline: *(3) April 30, Aug. 31, Dec. 31, 1976*

A variety of antigenic serum components have been reported to be uniquely present, or present in

elevated or decreased quantities, in the ser of cancer patients, as compared to other patients or to normal individuals (e.g., peptide hormones, virus antigens, B2 microglobulines). NCI is interested in evaluating assays that have potential for the immunodiagnosis of cancer and seeks laboratories that have developed a serologic assay which distinguishes cancer patients from those with benign disease and normal individuals. RFP is available to, and proposals will be accepted from, those who meet the following prerequisites:

a) Supply preliminary data documenting a useful test, together with a request for a coded serum panel, to the following address:

Immunodiagnosis Serum Panels,
Building 8, Room 118
National Cancer Institute
National Institutes of Health
Bethesda, Md. 20014

b) If NCI finds that the preliminary data supplied supports the assay's ability to discriminate between cancer patients and controls, NCI will supply the requestor with a coded panel of sera with which to test the assay, and further instructions as to its use and return for evaluation by NCI. If the assay gives distinguished performance on the serum panel, NCI will send an RFP to requestor.

RFP NCI-CB-64020-31

Title: *Diagnostic applications of antibodies to microorganisms and/or their natural products*
Deadline: *Jan. 26*

NCI seeks laboratories with documentable evidence of antibodies to bacteria, oncogenic viruses, other viruses or their products that cross react with human tumors and who have a suitable assay system developed for such cross-reactivity. Relevance to human disease must be described.

RFP NCI-CB-64021-31

Title: *Diagnostic application of human tumor or organ-associated antigens*
Deadline: *Jan. 26*

NCI seeks laboratories with documented evidence of new antigens (i.e., different from CEA or AFP) or antibodies with specificity for a particular tumor organ type. Detailed summary of such evidence must accompany proposal.

RFP NCI-CB-64023-31

Title: *Cells involved in the immune response to tumors*
Deadline: *Jan. 30*

NCI wishes to support investigations of the role of cell interactions and/or an analysis of the function of individual subpopulations in the generation and/or suppression of immune response to tumor cells. Studies of the role of anti-tumor cell antibody or non-specific immunoglobulin in facilitating or suppressing immune responses to tumors may also be supported.

Contract Specialist for all of the above immunology RFPs: Robert Townsend
Biology & Diagnosis
301-496-5567

RFP NCI-CM-67062

Title: *Structure-activity studies among anticancer agents. Linear free energy relationships*
Deadline: *Approximately Jan. 19*

The Laboratory of Medicinal Chemistry & Biology, Div. of Cancer Treatment, NCI, is seeking organizations not affiliated with chemical and pharmacuetical industries, having capabilities and facilities for the study of structure-antitumor relationships among members of various classes of antitumor agents. The approach to be applied in this particular project is the use of linear regression analysis to develop linear free energy relationships (LFER). The objective of the project is the use of the correlations developed to suggest structural modifications which will maximize antitumor activity and/or minimize toxic side effects within a series of congeners.

The contractor selected will be expected to apply LFER techniques whichare suitable to NCI chemical and biological data. It also will be expected to apply the synthetic and analytical techniques necessary to measure any required chemical and physical parameters, e.g. partition coefficients, electronic and steric constants, where they are not already available in the literature. The contractor selected will be expected to develop correlations within drug classes selected by the project officer. Antitumor data may be furnished by the project officer or be available from another source. When correlations are developed the contractor will be expected to provide suggestions with respect to possible drug modifications. The principal investigator must have extensive experience in LFER structure activity correlations and substantial experience in the area of drug design together with evidence of the successful application of quantitative structure-activity techniques.

It is anticipated that the total project will require two technical man years of effort per year.

Contract Specialist: W.T. Harris
Cancer Treatment
301-427-7463

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