THE CANCER LETTER

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NCI VIRUS PROGRAM HAS "IMPORTANT EXTENSION OF VIROLOGY" AS NEW APPROACH TO ETIOLOGY

A "new theoretical and intellectual framework with which to approach the human cancer problem" was reported to the National Cancer Advisory Board by Edward Scolnick, acting chief of NCI's Laboratry of Tumor Virus Genetics.

Scolnick's presentation was titled "Transformation Genes of RNA Tumor Viruses: A New Approach to the Etiology of Human Cancer." Excerpts follow:

(Continued to page 2)

In Brief

NIH INTRAMURAL RESEARCH SAID NEEDING BETTER PEER REVIEW, CHANGE IN SELECTING COUNSELORS

IMPROVED PEER review of NIH inhouse research has been suggested as a need at least equal to that of the grants peer review system. Ruth Kirschstein, director of the National Institute of General Medical Sciences, is heading a grants peer review study team. She has received at least two communications calling for improvements in the review of the work of NIH scientists. Joseph Melnick, Baylor, said that the various Boards of Scientific Counselors do not conduct in-depth evaluation of intramural research. "The detailed care and thoughtfulness with which non-NIH scientists must prepare proposals is, to my knowledge, in marked contrast to the abbreviated proposals submitted by NIH scientists," Melnick said. W.D. Armstrong, acting director of intramural research at the National Institute of Dental Research, suggested major changes in the structure of the Boards of Scientific Counselors. Appointments to boards now depend to some degree at least on sex, geographic distribution and minority factors, Armstrong said. "The result is that counselors . . . of expertise to evaluate a given laboratory are not available in sufficient numbers to make an effective review." He suggested naming a chairman and cochairman for each Board, with ad hoc members to be brought in for review of each lab. . . . **AMERICAN RADIUM** Society's 58th annual meeting, May 9-13 in Vancouver, will include: Presidential Address by Felix Rutledge, M.D. Anderson, on "The Estrogen Risk"; Residential Award Paper, "The Effect of Thymosin In Vitro on T Cell Levels During Radiation Therapy," by Daniel Kenady, Richard Simon and Paul Chretien, NCI; and the Janeway Lecture, "Pediatric Cancer Treatment: A Model for Oncology," by Audrey Evans, Philadelphia Children's Hospital. . . . **GERALD MURPHY**, Roswell Park director and chairman of the National Prostate Cancer Project, told the Senate HEW Appropriations Subcommittee that the budget projection for the project starting in 1976 totaled $30.8 million for the 1976, 1977 and 1978 fiscal years, more than twice the amount the project is scheduled to get—$14.6 million. The project supports more than 50 active grants.

CHEMICAL CARCINOGENESIS, VIRAL ETIOLOGY MAY BE SAME—RAUSCHER

(Continued from page 1)

For the past five to six years, the emphasis of research supported by the Virus Cancer Program on RNA tumor viruses, has been on the basic and applied aspects of the replication of RNA tumor viruses. With the discovery of the reverse transcriptase of RNA tumor viruses by Temin and Baltimore in 1970, the questions of the replication cycle of RNA viruses became clear enough in a theoretical framework to attempt to study the replication of these viruses and to try to apply the knowledge to the detection in human cancer cells of an RNA tumor virus. Many attempts have been made to isolate from human cancer cells either a complete replicating RNA tumor virus or to identify in human tumor cells a nucleic acid or protein that was a product of a replicating RNA tumor virus.

To this end, elaborate and very sensitive assays were developed for the detection by hybridization methods of nucleic acids of RNA tumor viruses and sensitive radioimmunoassays for the detection of various proteins in an effort to provide inroads into diagnosis or etiology of human cancer. I would like to reemphasize that these studies were predicated on the assumption that one would be looking for the product of replication of an RNA tumor virus. By this I mean the following: RNA tumor viruses contain approximately seven proteins that are part of the structure of replicating virus. Over the past six years the proteins have been isolated, purified and assays could be developed to detect them in cells carrying virus. Although a great deal of information has been learned regarding the natural occurrence of RNA tumor viruses in both avian and mammalian species, and even in some primates, these approaches have not yet provided a major insight into the etiology of human cancer.

Because of this, for the past two to three years, while these other approaches were going on, the Virus Cancer Program has been supporting on a smaller scale, research into the other major question in RNA tumor virology: that is not how viruses replicate, but how RNA tumor viruses actually cause malignant transformation. It seemed reasonable to simultaneously develop approaches to detecting viral genes involved in transformation. Such work has been going on in both the avian and mammalian system.

RNA tumor viruses can be arbitrarily subclassified into two major types of viruses. The first variety we will call strong transforming viruses or strongly oncogenic viruses. The reason for this subclassification is of the utmost practical importance in the field currently in terms of studying the question of transformation. In the first category, several strains of virus have been isolated which can rapidly and reproducibly transform cells in culture, and when injected into animals within a few days to a week or two, produce a malignant tumor in the animal. Some varieties of these viruses cause solid tumors in animals and are called sarcoma viruses; some varieties cause leukemias in animals. Examples of this are the Rous sarcoma virus in chickens, or the Friend leukemia virus in mammalian system, or the Abelson leukemia virus of mice from many types of biological and genetic experiments. One can be quite confident in studies on these viruses that (1) the virus causes a direct malignant transformation of cells, and (2) that the virus itself makes a protein responsible for the transformation of the cell.

In category two of transformation properties of RNA tumor viruses, we are dealing at the moment with the standard kind of late lymphatic leukemia viruses as typified by the Gross leukemia virus or Gibbon or woolly monkey leukemia virus and the mammary tumor virus of mice. These viruses, although clearly oncogenic, produce their oncogenic effect in animals only after long latent periods in the animal and have not yet been able to be shown in cell culture to directly transform cells. Therefore, although we have been able to study their replication, the study of their oncogenic property is difficult to perform experimentally.

"We are looking not for whole virus, but for expression of oncogenic proteins coded for by endogenous transforming viruses which are replication defective. . . . I believe we will find . . . we are just beginning to scratch the top of the true viral etiology for cancers"

With this background then, we have been studying the class one viruses, in particular in the mammalian kingdom, with regard to the nature of their oncogenic property. Similar studies have been carried out in the avian system by Peter Duesberg, Peter Vogt, Michael Bishop and Harold Varmus over the past three or four years.

Using the standard mechanisms for generating DNA copies of the RNA genome of RNA tumor viruses, we synthesized a DNA probe from the complete virus containing within the probe information homologous to regions responsible for both viral replication as well as regions of the virus responsible for transformation. Since the regions of the genome that were responsible for replication are in approximately tenfold excess over the regions responsible for transformation, if one simply utilized the whole probe generated in this reaction, less than 10% of the marker one had would be the region one would be interested in, and this would make experiments very difficult. Therefore, in order to enrich for the regions responsible for transformation in the probe, we utilized a

technical trick in order to remove the part of the probe that we were not interested in, the part responsible for replication and leave us with the part responsible for transformation.

By this kind of method, we have been able to generate probes which represent and allow us to measure the nucleic acid sequences of RNA tumor viruses responsible for their ability to transform cells.

Given that we have had these probes, we have begun to ask questions about what are the nature of these sequences hoping to find out about (1) the origin of these strongly transforming viruses, (2) the nature of the sequences which code for tranformation, and (3) ultimately, identification and isolation of the proteins actually responsible for turning a cell from a normal cell into a cancer cell.

The probe that we have had for the longest period of time is from the Kirsten and Harvey sarcoma virus, and this system is currently the best studied of the three systems and we will focus our attention on the general things learned from this system.

Several points I would like to make about the sequences of the Kirsten and Harvey virus that seem to be responsible for their oncogenic properties. These points are made: First of all, the sequences are not homologous to standard mammalian type-C nucleic acid sequences. That is, a probe representing the oncogenic sequences, in fact, will not detect the sequences in any mammalian type-C virus responsible for replication in these viruses. More importantly, the converse is also true and this is of critical importance if one thinks about the problem of identifying an etiologic agent in human cancer. The nucleic acid probes used by virtually all workers in the field for the past five or six years would detect only the products of replication. These probes will not detect the oncogenic sequences of the virus. Therefore, if one had a situation in humans, and there are many examples of this in animal models, where one had no replicating virus, but nevertheless the virus was responsible for the oncogenic properties of that cell, given the kinds of probes that have been used up to this point, one would not have diagnosed the cause of transformation in that cell as being of viral etiology.

Second, the proteins coded for in any of the standard assays would also not detect and not cross react with the proteins coded for by these oncogenic sequences. Third, the oncogenic sequences have been found to be part of normal DNA in normal cells. The isolation of these sequences as whole virus is rare and requires a recombination between a nononcogenic type-C virus and these sequences. But sequences themselves are common. The key then to natural cancer in the absence of replicating virus, is the expression of these sequences and what regulates that.

Lastly, we have found that these sequences are a new unique class of endogenous virus which almost never makes a whole virus. They are not a cellular sequence. Therefore, having these probes enables us to examine cells in a really novel way now to ask questions about the viral etiology of cancer, particularly in cells which are not producing replicating virus or viral particles. Now we are attempting to ask whether a virus can transform the cell, and we are not requiring the virus to replicate in order to identify it.

With these probes generated in the rat system, an illustration of the powerfulness of the probe generated is shown in examination of certain tumors from rats: One, a testicular carcinoma of rats spontaneously occurring in a Fischer rat intratistular tumor. Secondly, a chemically induced uterine carcinoma, induced in one strain of rats with DMBA. Thirdly, a plasma cell induced with mineral oil.

These tumors were examined by nucleic acid hybridization for the standard replicating nucleic acid of rat type-C viruses and with the probe that we have generated specific for oncogenic sequences of endogenous to rats. With the results of these experiments . . . certain important points become clear. (1) The levels of typical replicating viral RNA in the transformed uterine carcinoma cell which workers have shown that rapidly produces malignancies in animals are very low and in fact are not distinguishable from the levels of this same information in a control nontumorgenic uterine cell. In contrast, the oncogenic sequences in the low cell are very, very low and the high tumorgenic cell very, very high. Clearly, if one had been examining this chemically induced tumor cell with the standard nucleic acid probes for replication virus, one would not have identified this as relating viruses to the transformation of that in these cells. Similarly, one could have done the same experiments in the interstitial tumor of the rat or in one plasmacytoma tumor cell induced by the mineral oil.

The standard rat cell producing rat type-C virus reacts very well in this assay, but all of the tumor cells inducated, which have the high oncogenic virus-specific RNA, failed to react in this assay and again would have been identified as a virus-negative tumor with no clear etiology being related to the viral sequences. Therefore, one can identify a class of cells which do not produce viral particles, but which can be shown to have high levels of RNA homologous to the transforming sequences of known oncogenic type-C viruses. Having this type of probe opens up for us completely new vistas in examining transformed cells and trying to identify a viral etiology in transformed cells. This is in either spontaneously occurring or chemically induced tumors.

What about the theoretical relevance of this to human cancers? Human cancers clearly do not have high amounts of particles produced in them; in fact, this fact has frustrated RNA tumor virologists for years. Thus we now have a new theoretical and intellectual framework with which to approach the human cancer problem. We are looking not for whole virus, but for expression of oncogenic proteins coded for by

endogenous transforming viruses which are replication defective. As we develop assays for these proteins and nucleic acid sequences in man, we can begin to think about finding high risk groups and early diagnostic tests for the presence of oncogenic markers. I think vaccines against standard types of viruses are less likely to be useful.

From a practical point of view, we also have an immediate approach to developing such diagnostics in the human situation which is being worked on with this model system as basis. RNA tumor viruses isolated from the woolly monkey which you have heard about in the past were both a class 2 virus, that is, a weakly oncogenic virus, called the woolly sarcoma virus. Up to now, again, people have not had probes representing the oncogenic sequences of the woolly sarcoma virus. We are in the process of applying the same approaches which we have applied to the Kirsten, Harvey and Moloney sarcoma virus and that others have applied to the Rous sarcoma virus in an attempt to obtain a probe specific for the oncogenic sequences of this primate oncogenic virus.

I believe that we will find as we have in the rat system, as we generate such oncogenic sequences specific probes that we are just beginning to scratch the top of the true viral etiology for cancers in a situation which we have never been able to examine before, cells that are not producing virus particles nor any of the markers for viral replication.

"This is why viruses have got to be considered environmental carcinogens," commented NCI Director Frank Rauscher following Scolnick's presentation. "It makes no sense to take money out of the virus program and put it into chemical carcinogenesis. They both may be the same thing."

NCAB Member Harold Amos said the work reported by Scolnick "is extending virology in an important way."

FDA HAZLETON PROBE FINDS SOME PROBLEMS; TEST RESULTS UNAFFECTED

FDA investigators probing operations of Hazleton Laboratories reported finding certain deficiencies in the conduct of some animal tests but came up with nothing as serious as the charges they previously had made against G.D. Searle Co.

Hazleton is one of NCI's largest contractors, conducting about $5 million a year in bioassays, much of it as a subcontractor to the Carcinogenesis Program prime contractor, Tracor Jitco. The firm does about $1 million work a year for other NIH institutes, and performs tests for a wide variety of organizations around the U.S. and internationally, including most of the major drug manufacturers.

Searle had been charged (*The Cancer Letter*, Jan.) in testimony before Sen. Edward Kennedy's Health Subcommittee with a range of practices that led FDA to question the scientific data of the company submitted to support new drug applications. So serious were those charges that a federal grand jury is looking into them for possible criminal violations.

Since Hazleton has frequently performed bioassays for Searle, FDA decided to take a look at tests of three compounds commissioned by Searle - aldactone, flagyl and aspartane. FDA investigators spent two months at Hazleton, meticulously going through all records in those studies.

The worst they could find was that:

- A certain number of autolyzed tissues (tissues improperly preserved) had been included in the statistical analysis. One newspaper quoted FDA investigator Adrian Gross as saying it was a "large number." However, *The Cancer Letter* learned that it was only a handful out of thousands of tissue samples and nowhere close to the number that would have affected the results of the studies. In fact, neither Gross nor FDA Commissioner Alexander Schmidt would say that any of the deficiencies were serious enough to have changed the outcome.
- Failure to scientifically test the compounds given to the animals or to test their food for any variations. Such tests were not in the protocols and generally have not been included in animal testing protocols anywhere. They may soon become standard practice, since many scientists feel that such variations could contribute to tumor incidence differentials and thus distort test findings.
- Failure to adequately review test records or to verify their accuracy. Although Hazleton officials feel their record keeping was as good as anyone's, and good enough to satisfy outside reviewers, including the meticulous and constant overview of NCI project officers, they have taken steps to improve it.
- Reporting tumors for which slides had not been made. If that had involved a substantial number of tumors, it might have affected the results of the studies, but on the side of safety, indicating that the compound had caused more tumors than it actually did. But again, the number of such instances - five reported by the FDA investigators - was statistically insignificant. Upon rechecking, Hazleton found that three of the five had been the result of typographical errors in the reports.

Donald Nielsen, Hazleton president, expressed displeasure that his firm's responses to the investigation were not included in Schmidt's testimony to the Kennedy subcommittee. Nielsen issued a statement on the matter:

"The management and staff of Hazleton Laboratories America Inc. have not had the opportunity to review the final report submitted to Dr. Schmidt by the investigating task force. We will endeavor to receive a copy of that report and study its contents in detail.

"At this time, however, we must say that the references to Hazleton Laboratories contained in the state

ment submitted to the subcommittee contained incomplete and misleading statements which did not incorporate all of the facts relative to the studies conducted by Hazleton Laboratories for G.D. Searle.

"Three teams of investigators collectively spent two months at Hazleton, reviewing the complete files on studies conducted on only three compounds. These investigations raised several questions which were discussed and, we thought, satisfactorily answered prior to the departure of the respective investigating teams. Our responses were also put in writing and provided to each team. Unfortunately, only the questions which they raised and none of the answers we gave were contained in the statement presented to the subcommittee.

"Some weeks ago we advised the FDA that we would be happy to cooperate with them in any further study they may wish to make of our facilities, personnel and procedures. We know that our staff maintains the highest standards of scientific integrity in all their work, and as a company we have followed a policy of having regular external evaluations made of our facilities and staff. For example, we are one of the few contract research organizations which is inspected and accredited by the American Assn. of Laboratory Animal Science; our clinical chemistry laboratory and microbiology laboratory are inspected and licensed by the Communicable Disease Center in Atlanta, Ga.; and three of our five pathologists have passed the certification examination conducted by the American College of Veterinary Pathologists. In addition, three members of our staff are diplomates in the American College of Laboratory Animal Medicine, and they semi-annually conduct internal training programs on laboratory animal medicine for our technical personnel.

"These facts make us feel that Hazleton Laboratories is one of the finest contract research organizations in the country, and we are continuing to make every effort to support that contention."

WHOLE BODY HYPERTHERMIA SYMPOSIUM SCHEDULED BY NCI FOR JUNE 7-8

NCI's Div. of Cancer Treatment has scheduled a two-day symposium on whole body hyperthermia for June 7-8. It will be held in NIH Building 31 Conference Room 6, starting at 9 a.m. each day.

Topics will include the physiological, toxicological, pharmacological and instrumental aspects of physically induced whole body hyperthermia as employed in cancer treatment. The entire symposium is open.

The DCT Board of Scientific Counselors has approved a list of top priority hyperthermia projects (*The Cancer Letter*, March 26) which ultimately will be developed into grant and/or contract programs. These projects probably will be designed to determine normal tissue response to hyperthermia plus radiation or chemotherapy; how heat modulates radiation or chemotherapeutic response; the production and control of localized hyperthermia and resulting thermal distributions in vivo; and the pathology and upper limit of tolerance of systemic hyperthermia.

NEW CREGS ANNOUNCED IN EPIDEMIOLOGY, VIRUS, CARCINOGENESIS RESEARCH

Six new Cancer Research Emphasis Grant (CREG) announcements have been made by NCI seeking research proposals in viruses, carcinogenesis and epidemiology.

Applications should be submitted on NIH Form 398. The application and covering letter should include title and number of the CREG. Mail to Div. of Research Grants, NIH, Bethesda, Md. 20014.

CREGs are open to nonprofit organizations and institutions, state and local governments and their agencies, authorized federal agencies, and individuals according to NIH grant policies. Applicants may elaborate on the purposes, objectives, rationale, and significance stated in this announcement and must complete portions of the application pertaining to procedural details, the investigator's related experience, facilities available, budgets, and biographical information for key professional personnel.

DCCP - 17

Title: *Malignancy induced by small DNA viruses (adenoviruses or papovaviruses)*

Deadline: *Oct. 1 for study section review in February and National Cancer Advisory Board review in May, 1977*

NCI is accepting applications for support of research on the interaction between small DNA viruses and cells as it relates to malignant transformation. This area of research includes: (1) the study of viral and cellular genes governing permissiveness and viral transforming functions, (2) the study of molecular events leading to virus-induced malignant transformation of cells, (3) the interaction of small DNA viruses with the type C RNA viruses or with other classes of known or suspected carcinogens in relation to cell transformation.

Applicants should propose an individual project with a level of effort corresponding to approximately one professional man-year.

Project Director: Elke Jordan
Cause & Prevention
301-496-6927

DCCP - 18

Title: *Herpesvirus-induced malignancy*

Deadline: *Oct. 1*

NCI is accepting applications for support of research on the interaction between herpesviruses and cells as it relates to malignant transformation. This area of research includes: (1) the study of viral and cellular genes governing permissiveness and viral transforming functions, (2) the study of molecular events

leading to virus-induced malignant transformation of cells, (3) the interaction of herpesviruses with the type C RNA viruses or with other classes of known or suspected carcinogens in relation to cell transformation.

Applicants should propose an individual project with a level of effort corresponding to approximately one professional man-year.

Project Director: Elke Jordan
Cause & Prevention
301-496-6927

DCCP - 19

Title: *Metabolism and mechanism of action of carcinogenic organohalogen compounds*

Deadline: *Oct. 1*

The Carcinogenesis Program of the Div. of Cancer Cause & Prevention is interested in developing additional research in the area of the metabolism and mechanism of action of carcinogenic organohalogen compounds. The objective of this research is to study the reactions that are necessary for this group of compounds, or individual compounds, to produce a carcinogenic response in mammalian species. In particular, information is desired on carcinogenic halogenated aliphatic and aromatic compounds in respect to the following:

1. The identification and site of formation of the proximate and ultimate carcinogenic metabolites.
2. The identification of cell constituents, e.g., the macromolecules, which are altered as a result of their interaction with the test compounds.
3. The mechanism of interaction between the test compound and the altered tissue constituents.

Applicants should name the compounds proposed for study. These may include both carcinogens and noncarcinogenic structural analogs. Examples of short chain halogenated alkanes and alkenes that are of interest are trichloroethylene, carbon tetrachloride, and chloroform; while cyclic ones might be DDT, chlordane, or dieldrin.

Project Director: Elizabeth Weisburger
Cause & Prevention
301-496-5688

DCCP - 20

Title: *Effects of aging on susceptibility to carcinogens*

Deadline: *Oct. 1*

NCI is accepting applications for support of research projects that will attempt to define aging-associated factors that have a reasonable likelihood of influencing the susceptibility of cells to carcinogenesis. Two hypotheses are among those to be considered relevant to this concept: (1) the age of host at the time a carcinogenic stimulus comes in contact with the target cell strongly influences cell susceptibility (as inferred from age-associated incidence tables) and (2) irrespective of the time in life at which the carcinogenic stimulus is experienced, certain age-associated changes serve as promoters or activators of that stimulus and effect histologically observable cell alterations and growth. Preference will be given to those studies in which quantitative measurements can be made of parameters that are known to occur or change during aging or can be strongly justified by inference from existing data to have significance to carcinogenesis.

NCI is currently aging two colonies of laboratory rats, an inbred AxC strain and a random-bred Sprague-Dawley strain. These have been derived by germ-free procedures, have been exposed to a defined bacterial flora and are being housed under barrier conditions during aging. Shortly after project award, a limited supply of these rats will be available up to 16 months of age. Distribution, however, will be severely limited in order to allow aging in excess of 30 months. Consequently, investigations initiated in approved and funded grants awarded from this announcement must utilize other existing colonies of aged animals (not necessarily rats), to develop a background of knowledge which will more clearly define aging factors associated with cancer induction and which will assist in establishing priorities for use of the above-described colonies of rats being developed. Aged animal colonies, generated for other research purposes, are in existence and are known to be available for other experimental studies. As the availability of the NCI-aged rat colonies becomes more available, all investigators participating in this program will be informed of their availability and the procedures by which they can be obtained.

Proposals from individuals or groups with capabilities and experience in carcinogenesis and related fields are desired. Within the general program goal described above, applicants should define specific aims and describe experimental procedures in support of those objectives. Applicants must clearly indicate the availability to them of sufficient numbers of animals (not necessarily rats) at those ages appropriate for the proposed experiments. High-quality animal facilities and care are required to permit adequate survival. Records should be submitted indicating survival rates at various ages approaching the maximum life span of the proposed experimental species. Preference will be given to species having known spontaneous or inducible neoplasia in organs of high relevance to human cancer incidence and mortality. Although such factors as hormonal influences and cytogenetic changes are clearly relevant, an analysis in greater depth, e.g. at the biochemical level, is desired. Three years' support is contemplated with encouragement of renewal based upon progress made. Proposals should develop a study rationale for a sequence of approaches over the three-year period.

Project Director: Richard Pledger
Cause & Prevention
301-496-5471

DCCP - 21

Title: *Reasons for variation in cancer patient survival by race*

Deadline: *Oct. 1*

NCI is accepting applications for support of research projects designed to increase knowledge concerning the basis for variation by race in cancer patient survival. For many forms of cancer, the survival experience for white patients is more favorable than that for black patients even when the disease is considered localized at diagnosis. Furthermore, a higher percentage of black patients than whites have metastatic disease when cancer is first discovered.

Research in this area might include sociocultural parameters in an attempt to explain possible differences by race in delay from onset of disease to cancer diagnosis. Studies of recurrence and/or patient survival must take into account variables of known prognostic and etiologic significance, e.g. histologic type, extent of disease and other demographic, morphologic, and physiological descriptions of neoplasm and host. Proposals should be oriented toward specific forms of cancer and should include detailed plans for data collection and statistical analysis.

It is anticipated that the project period will not exceed five years, and that the level of effort per year will approximate one to two professional man-years.

Project Director: James Murray
Cause & Prevention
301-496-3116

DCCP - 22

Title: *Cancer epidemiology in collaboration with the NCI program of Cancer Surveillance, Epidemiology and End Results (SEER)*

Deadline: *Oct. 1*

NCI is accepting applications for support of research projects in the field of cancer epidemiology and etiology which will be conducted in collaboration with cancer registries particiapting in the SEER program of cancer Surveillance, Epidemiology and End Results. The SEER program provides information on trends in the incidence of the various forms of cancer, variation in the occurrence of cancer among different population groups and in different geographic areas, changes in general treatment tractice and the associated cancer patient survival patterns. Data are obtained from a selected number of population-based cancer registries that provide uniform information on a continuing basis and participate in ad hoc studies designed to identify and assess etiologic and prognostic factors.

Only limited pilot or feasibility studies can be supported under the present contract agreements with the participating registries. Therefore, NCI is now soliciting full-scale comprehensive CREG research proposals for analytic studies in etiology and/or prognosis for any form of cancer. Of special interest are research projects which may lead to identification of factors which can be modified to reduce the incidence and mortality of cancer. Purely descriptive studies are not desired. Although specific research protocols are requested, the actual approaches and methods will be left to the initiative of the applicants. Studies may be either retrospective or prospective in design.

Project Director: James Murray
Cause & Prevention
301-496-3116

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-CM-77101

Title: *Iso-antigenic typing of mouse strains and tumors*

Deadline: *May 20*

Services of organizations having the necessary scientific and technical personnel and physical facilities to conduct iso-antigenic typing of mouse strains and tumors. The activities involved in performance of this contract can be divided into three areas as follows: Perform reciprocal skin grafts between mice of various strain sublines and counter parts from the NIH colony as referenced material. The mice shall be observed for 90 day periods in order to detect minor histoincompatibilities. It is estimated that there will be approximately 21 strains of mice from about 77 colony sources totaling approximately 900 grafts.

Perform a controlled study in order to determine an approach to the immunogenetic characterization and monitoring of the various sublines and NIH reference animals that will be less time consuming, more sensitive and hopefully less expensive than those that are presently being used.

While the successful offeror will be given considerable leeway regarding the type of assay for this study, it is anticipated that consideration would be given to at least some of the following: (A) mixed lymphocyte reaction, (B) cytotoxicity, (C) hemopoietic grafting, (D) H-2 typing.

Candidate organizations must have the capability of (A) Characterizing the karyotype of murine tumors used for compound evaluation studies. (B) Testing the H-2 histocompatibility antigens of tumors and hosts by means of iso-antisera (produced by the contractor). (C) Testing standard tumor lines for antigenic identity after recovery from the frozen tumor bank.

Contract Specialist: D.M. Abbott
Cancer Treatment
301-427-7463

QUESTIONS ASKED, ANSWERED RELATING TO VIRUS CANCER PROGRAM RFP

A number of questions have been raised by prospective bidders concerning a Virus Cancer Program RFP (NCI-CP-VO-61029-66), "Studies of molecular events leading to transformation by RNA oncogenic viruses." Clyde Williams, NCI contract specialist for the project, compiled the following list of questions asked and his answers to them:

1. What type(s) of transplantable tumor lines will be used; that is, low, moderate, or high risk viruses?

—Only a few of the tumor lines to be carried in the mice are viral induced. Others may be spontaneously induced or result from carcinogen induction, etc. Usually, manipulation of these tumor lines would involve low, or at most, moderate risk viruses.

2. Will certain of the 15 to 20 tumor lines require subdivision of a species into separate rooms, or will an adequate cage marking system be sufficient, provided that species are separated by room?

—Maintenance of the transplantable tumor lines will not require separate rooms.

3. Will the experimental protocols require technical services, inoculations, or transportation on weekends?

Sometimes.

4. Will animals be returned to NIH only at the end of the appropriate time interval, or will certain animals return to the holding facility numerous times during a specific experiment?

—Manipulation of the animals, including necessary transportation will be depended upon specific experimental protocol to be provided by the project officer.

5. Will all material for incoluation or testing be prepared and provided by NCI?

—Initial seed or stock material will be provided by NCI. However, the contractor will be required to provide appropriate technical services.

6. Will specific testing procedures and/or protocols be provided by the project officer; that is, quality control requirements for skin test antigens?

—Yes.

SOLE SOURCE NEGOTIATIONS

Proposals are listed here for information purposes only. RFPs are not available.

Title: SEER and Third National Cancer Survey data processing services
Contractor: Geomet Inc., Gathersburg, Md.

Title: Housing and maintenance of a chimpanzee breeding colony
Contractor: Southwest Foundation for Research & Education.

CONTRACT AWARDS

Title: Evaluation of antitumor properties of streptovaricin
Contractor: New York State Dept. of Health, $96,312.

Title: Administrative support services
Contractor: Georgetown Univ., for continuation and expansion of administrative support services relative to the activities of the Eastern Cooperative Oncology Group, $499,860.

Title: Screening of compounds for antitumor activities
Contractor: Litton Bionetics, $62,793.

Title: Resynthesis of drugs and chemicals
Contractor: Monsanto Research Corp., $583,900.

Title: Operation and maintenance of the drug distribution system
Contractor: Value Engineering Co., $193,592.

Title: Viral studies for cancer chemotherapy patients
Contractor: Georgetown Univ., $181,360.

Title: Replication of oncogenic RNA viruses
Contractor: Columbia Univ., $312,428.

Title: Application of advanced optical and electrical technology to oncology problems
Contractor: General Electric Co., $64,080.

Title: Tumor registry training program
Contractor: Univ. of California (San Francisco), $28,597.

Title: Expansion and evaluation of the telephone cancer public information system – Can-Dial
Contractor: New York State Dept. of Health, Roswell Park Div., $22,000.

Title: Mechanisms for cell-mediated destruction of tumor cells
Contractor: Johns Hopkins Univ., $161,650.

Title: The isolation of antineoplastic agents from plants
Contractor: Univ. of Illinois, $338,250.

The Cancer Letter—*Editor* JERRY D. BOYD

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