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NCI Looking At CCOP Budgets To Determine How Many Will Be Funded; Some Top Scorers Identified

Now that the month long review of Community Clinical Oncology Program applications has been completed, NCI staff in the Centers & Community Oncology Program of the Div. of Cancer Prevention & Control is analyzing budgets of those likely to fall in the funding range in an attempt to determine how far the $10 million earmarked for the program

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In Brief

ACS Seeking Candidates For Holleb Replacement; NCI To Recruit AD For Biological Carcinogenesis

AMERICAN CANCER Society is conducting a national search for a senior vice president for medical affairs, the position held by Arthur Holleb, who will retire June 30 after 19 years with the Society. Candidates must have: an MD with a license to practice in at least one state; ability to administer a large complex medical organization; a national and international reputation in cancer control; an understanding of the role of basic and clinical research; ability to publish articles in oncology literature; an understanding of the staff/volunteer concept through which ACS operates. The position requires travel 60-70 percent of the time. ACS will accept nominations through April 30. Send CVs to Search Committee SVMA, ACS, 4 West 35th St., New York 10001, Attn: M.J. Zajac, National Vice President for Personnel. . . . **ANOTHER NATIONAL** search is on, by NCI's Div. of Cancer Etiology for an associate director to head the Biological Carcinogenesis Program. DCE Director Richard Adamson said a search committee would include both government and non-government scientists, including some members of the division's Board of Scientific Counselors. Adamson has been acting head of the program since it was established more than two years ago. With the transfer of Robert Gallo's Laboratory of Tumor Cell Biology into DCE along with the move of NCI AIDS vaccine development activity into that division, the Biological Carcinogenesis Program requires the full time attention of a "highly qualified" scientist, Adamson said . . . . **JOHN HORTON**, former president of the American Assn. for Cancer Education, has retired as head of oncology at Albany Medical College. He will remain as professor of medicine and in a clinical capacity. **JOHN RUCKDESCHEL** has been named to replace Horton as head of oncology.

Twenty Two CCOPs Identified Which Appear To Be Within Funding Range

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will go. Meanwhile, priority scores of about one third of the applicants became available as they were requested by principal investigators and were passed on to **The Cancer Letter**. Twenty two appear to be within what should be within the funding range, although the payline now is anyone's guess.

The top 22 scores seen by press time this week were Columbus, OH; Binghamton, NY; Scranton, PA; Hackensack, NJ; Kalamazoo, MI; Wichita, KS; Eastern Maine; New Orleans; Tulsa, OK; Grand Rapids, MI; Atlanta (St. Joseph's); Dayton, OH; Portland, OR; Phoenix, AZ; Allegheny (Pittsburgh); CCOP of the Ozarks; Sutter (Sacramento); Springfield, MO; Springfield, IL; Kansas City (with Robert Belt as the PI); Central Los Angeles; and Mt. Sinai of Miami, FL.

Those all had scores of 228 or better. The payline during the first CCOP competition in 1982 was 260.

Since the amount of NCI funding for each CCOP will be determined to a large extent by patient accrual, Centers & Community Oncology Program staff will have to make some judgments about the first year budgets. They hope to have at least a preliminary reading on where the payline will by the end of this week or sometime next week.

Based on the assumption that the addition of cancer control research to CCOP activities would result in increased budget requests, guesses made before the review were that no more than 40-45 could be funded with the $10 million available. There are 57 active now.

Cutting the program that much would not be popular with anyone, especially the cooperative groups which are getting as many as half of their patients through CCOPs. Nor would it be acceptable to NCI executives, including Director Vincent DeVita, who had hoped the program could be expanded. It seems likely that NCI will add some money to the program, and Congress might well earmark some more in addition.

Once a payline has been established, the probability exists that it will be overlooked in one or two instances, to permit funding of a CCOP in an underserved area. There also may be a couple of cases in which very good CCOPs came up with relatively poor scores. NCI may choose to make an exception in those cases.

LAK-IL-2 Studies Continue Amid Controversy; Efficacy Boost Sought

Clinical studies of lymphokine activated killer cell-interleukin-2 at the six institutions selected to test the regimen developed by NCI's Steven Rosenberg had accrued 20 patients by early March since those trials were resumed in January. They had been suspended since late last summer, when some patients contracted hepatitis A from contamination of sera used in the process.

The source of the contamination was identified and traced to a single donor. Changes were made in the way sera is obtained and processed, and FDA permitted resumption of the trials.

The extramural study is now limited to patients with renal cell cancer, melanoma and favorable histology non-Hodgkin's lymphoma.

When the extramural trials were stopped, it appeared that they were not achieving the same remarkable response rates reported by Rosenberg in his intramural studies. Rosenberg felt that with the kidney cancer patients, at least, it was because extramural patients had greater tumor burdens. All of his patients had had nephrectomies, while nine of 31 extramural patients had not.

Robert Wittes, director of the Div. of Cancer Treatment's Cancer Therapy Evaluation Program which is supervising the extramural trials, made some further observations on the situation at the recent meeting of the DCT Board of Scientific Counselors.

"The intramural and extramural response curves are on top of each other, except for kidney cancer," Wittes said. "Dr. Rosenberg is convinced that his patients had lower tumor burdens. . . but we don't have any convincing evidence that tumor burden is having an effect." The numbers, 22 with nephrectomies, nine without, "are too few to compare. . . So we don't have an explanation for the difference."

The response rate for kidney cancer in the intramural trials is about 32 percent, twice that of the extramural studies before they were suspended.

Wittes said that "it is pertinent to expand the study to other malignancies, but most pertinent are efforts to increase efficacy. If this were a drug rather than a biological, you would say it is simply a nice drug, and interest probably would be less. But if you had a drug with this activity in renal cell cancer, we would be pretty

excited. There is no question, we need to continue. So how do we boost efficacy? The regimen is hard to give as originally designed. We decided to give IL-2 with LAK by continuous infusion. We had to decrease the amount of IL-2 initially because of toxicity. By giving more at the end, we were able to decrease the amount up front. There is the impression so far that this regimen is better tolerated, and we are fairly successful in getting in full doses of IL-2"

Board member John Mendelsohn questioned the advisability of expanding the study to include more types of cancer. "You have two targets, melanoma and kidney cancer, where the response is real. Shouldn't you learn how to give it better to the tumors that do respond before you start giving it for colon cancer and others?"

"I agreed with you the last time you said that," Wittes answered. "But when you see a good response in some patients, it is hard to resist." Rosenberg had obtained responses in colon cancer, although not as many as in kidney cancer and melanoma.

"We run out of room and options with some tumors," Clinical Oncology Program Director Samuel Broder said. "I would think we would want to target it in the common tumors."

"Isn't this in essence phase 1 data in chemoresistant tumors?" Board member Lawrence Einhorn asked. "Even 16 percent is impressive. In colon cancer, 12 percent is not bad. I know of no drug, except platinum, that had that much activity that early."

The Moertel Editorial

The editorial in the "Journal of the American Medical Assn." by Charles Moertel, calling for the end of the LAK-IL-2 studies, has drawn fire from all quarters at NCI.

Moertel is founder and former director of the Mayo Cancer Center, founder and chairman of the North Central Cancer Treatment Group, former member of a number of NCI advisory bodies, and seldom hesitates to criticize what he considers hasty conclusions and inadequate testing of cancer therapy. In the "JAMA" editorial, Moertel ripped NCI for (he said) publicizing the LAK-IL-2 results as a breakthrough and for minimizing the toxicity in its public statements. He said the trials were a waste of money and should be discontinued because the regimen is too toxic and is ineffective.

"I believe that Dr. Moertel has grossly misrepresented the nature and results of this work, and has done a disservice, not only to Dr. Rosenberg's research, but to cancer research and the public," DCT Director Bruce Chabner said. "To begin with, at no time did Dr. Rosenberg or any other member of NCI represent the work as a breakthrough or as a treatment ready for standard medical practice. It was a research observation, the first documented antitumor activity in man for a cellular immunotherapy. My colleagues and I repeatedly emphasized the preliminary nature of these findings, the need for confirmatory trials and improvement, and the significant toxicities associated, including death. . . [It is] my personal opinion that to end such work at this point on the basis of either cost or limited efficacy would make little sense. . . The preclinical investment in IL-2 and LAK cell research . . . clearly overshadows the cost of the clinical trial. To stop trials that, for the first time in this field, have produced clinical responses would be a waste of this tremendous investment. The realy question is efficacy. While the clinical efficacy is, at this time, limited to renal cancer, melanoma, and the few lymphomas tested, the therapy needs to be modified and tested in other diseases. . . Will LAK cell therapy be more effective if given with chemotherapy or given in the adjuvant setting? Preclinical studies would indicate so, but we will never know if we listed to Dr. Moertel."

Chabner said he agreed with Moertel's point, that the widespread use of experimental therapies in the practice of medicine would be inappropriate, "for IL-2/LAK or any other unproven method."

Chabner suggested who the real villain might be. "There is a problem with the media and its need to make stories larger than life. The dangers to responsible scientists are real, because of the potential that media inflation of legitimate stories will create unfulfilled expectations." But that should not "discourage us from reporting our results and standing behind them publicly."

Armand Hammer, chairman of the President's Cancer Panel who has taken special interest in Rosenberg's work (including awarding him his annual $100,000 prize last year), joined in the defense. At the recent meeting of the National Cancer Advisory Board (via a letter read by Panel member William Longmire), Hammer said, "I do not believe the author helped the cause of medical research by his unwarranted attack on NCI and Steve Rosenberg.

"Certainly neither Steve Rosenberg nor Vince DeVita have ever claimed the new protocol to be a breakthrough, as the editorial implies, Hammer continued. "The media may have used this term, but Vince and Steve cannot be held responsible for what the media does.

"Nor have extravagant claims been made for the effectiveness of the LAK-IL-2 protocol by those who developed it. I believe Dr. Rosenberg has treated his work responsibly all along, and the fact remains there have been encouraging, positive results. With additional research and continued clinical trials, there is every reason to believe that more positive results will be achieved in the future, both at NCI and at other institutions where it is being carried out."

Hammer cited the work of Richard Fisher, of Loyola Univ. in Chicago, where the Panel met in December. Fisher "presented a very convincing case. . . indicating that the toxicity [of LAK-IL-2] can be ameliorated by dose manipulation and patient selection and is not severe enough to warrant cessation of the trials. . . No one at NCI ever tried to hide or minimize this aspect of the treatment. The editorial, perhaps conveniently for its argument, failed to note that however intense the toxicity may be during the administration of IL-2, it can be rapidly reversed. Dr. Fisher told us that within 24 to 48 hours after stopping treatment, the patient recovers from the major side effects. This cannot always be said for either chemotherapy or radiotherapy."

At the DCT meeting, Dan Longo, director of the Biological Response Modifiers Program, commented that Moertel had "sat in on a BRMP site visit. He was very objective and fair. He offered some solid comments. It was my impression that he had no ax to grind."

The Cancer Letter offered Moertel the opportunity to re-rebutt his critics. He declined, but added, "I've had my say. I thought it was necessary to respond to public concerns. I did it in what I considered an appropriate manner. Debating this further would not be productive."

For the record: Chabner and Hammer were correct in that all of NCI's public statements seen and heard by **The Cancer Letter** included plenty of cautionary language on the preliminary nature of the results, toxicity, etc. However, NCI, Hammer and DeVita are at least partially responsible for the enormous media coverage. When Rosenberg first published his findings in the "New England Journal," NCI announced it in an embargoed press release, then invited the lay press to cover the NCAB meeting that week when Rosenberg presented his data. Hammer made a special trip to Washington to ask the President for more money to support development of Rosenberg's regimen, a fact he revealed on numerous public occasions and which stirred media interest. And DeVita's natural optimism and enthusiasm fueled that interest at every step.

Enthusiasm and optimism are what keep the Cancer Program going. Most of the articles in the lay press were factual and included the disclaimers, but cancer patients can't be blamed for looking for the "larger than life" aspects of a story.

DCE Board Approves Concepts For $6 Million In Contracts

More than $6 million worth of contract supported projects were given concept approval last week by the Board of Scientific Counselors of NCI's Div. of Cancer Etiology, including one new study of women exposed to x-rays for scoliosis.

Three of the concept approvals were for recompetition of existing contracts and another was for a noncompetitive extension of a contract with M.D. Anderson Hospital for radiation dosimetry for epidemiologic studies.

The Board disapproved the concept of recompeting a contract for cell culture support services for the Laboratory of Cellular & Molecular Biology.

The scoliosis study contract will cost an estimated $225,000 in the first year and a total of $965,000 over four years. John Boice, chief of the Radiation Epidemiology Branch, presented the concept to the Board:

> Studies of populations exposed to medical irradiation are an important resource for quantifying late radiation effects because exposures can be accurately estimated, nonexposed or minimally exposed patients are often available for comparison, and information on other risk factors can frequently be obtained from medical records.
>
> A major area of emphasis in the Radiation Epidemiology Branch has been to clarify the risks associated with radiation exposure to the female breast, one of the tissues most sensitive to the carcinogenic effects of ionizing radiation. Over the last several years we have conducted studies of patients monitored with multiple chest fluoroscopies for tuberculosis and of atomic bomb survivors. Comparative analyses have included patients treated with radiotherapy for postpartum mastitis. Recently we completed a pilot investigation of patients with scoliosis exposed to

multiple diagnostic x-rays during childhood and early adolescence. A two fold risk of breast cancer was identified which occurred primarily among women followed for more than 25 years. Estimates of radiation dose to the breast ranged from negligible to almost 70 rads. An extended study would allow us to clarify and quantify the risks of radiation induced breast cancer at an age of apparent high sensitivity and for which little data exist.

Because of the intense x-ray monitoring of persons with scoliosis that occurs around puberty, radiation risks could be determined not only with respect to age at exposure, but at the time of important biological processes, such as breast budding. Just recently, evidence of radiation induced breast cancer among girls exposed at a very young age has appeared from the studies of A-bomb survivors and of patients irradiated for enlarged thymus glands, but risk estimates are based on comparatively small numbers. The low dose, fractionated nature of the x-ray treatment in scoliosis, which would span several years, is a particularly attractive component of this investigation as is the ability to make very accurate estimates of organ doses to the breast and surrounding tissue.

Scoliosis is a common condition, with a prevalence of about two percent in the general population. The form of scoliosis that requires treatment is most common in girls. More than one half of the states conduct scoliosis screening programs, in some or all of their school jurisdictions, on children ages 9-14 years. Once detected, scoliosis requires periodic x-ray monitoring of the spine, especially during adolescence when the bones are growing at an accelerated rate. The time of breast budding is clinically important because it indicates that the growth spurt has or will soon begin. As such, the date of breast budding is commonly recorded in the medical records. Monitoring often includes full spinal x-rays with the child facing the x-ray tube, i.e., with the breast receiving the maximum dose possible.

A feasibility study was conducted in Minnesota in which 1,013 women with scoliosis were identified, records abstracted, persons located, and questionnaires completed. Some persons received over 600 roentgenograms during an average 10 year period to monitor the progression of spinal curvature and the effect of treatment. As recently as 1979 the average dose to the breast from one AP full spinal x-ray was on the order of 0.6 rad and the cumulative breast dose could range from 18-24 rad following a typical series of examinations. Multiple series would result in higher doses. There is current concern that exposures of this magnitude should be reduced. X-ray exposure for scoliosis is a public health issue, as well as a scientific one, because scioliosis is such a common problem and because multiple x-rays are most frequent during a susceptible time of life.

In the Minnesota pilot study, very preliminary estimates of dose to the breast indicate an average of over 10 rad and a range from 0 to about 70 rad. Forty three cancers were reported, including 11 breast cancers, one thyroid cancer and two leukemias. Less than six cases of breast cancer were expected based upon rates derived from the general population (observed/expected=1.84). No other tumors were in excess.

Objectives of the study will be to provide new and detailed information on the age specific risk of breast cancer following diagnostic radiation for scoliosis during childhood and early adolescence, to relate risk to important biological processes such as breast budding and menarche, and to assess the effectiveness of low dose x-rays given frequently over a period of several years in causing breast cancer. All cancers would be evaluated, but emphasis would be on the breast, leukemia, lung and thyroid.

A cohort of 7,500 additional women with scoliosis would be identified and cancer incidence and mortality would be determined from medical records, questionnaires and death certificates. The proposed methods would be guided by the experience of the feasibility study. Letters have been sent to the major clinics or orthopedic surgeons in the U.S. who have treated scioliosis for at least the past 30 years. The letters were sent under the sponsorship of the Scoliosis Research Society, which had given its approval to both the feasibility and the proposed study. To date, we have received information from and/or visited 15 hospitals/clinics that are willing to participate. Using conservative estimates, we have found that well over 10,000 women are available for study who would meet the study inclusion criteria. Hospitals selected for the proposed study would be based on available numbers, the type of diagnostic x-ray examinations yielding high breast doses, an the possibility of long term followup.

Information from the patient records would be abstracted on date of birth, race, family medical history, x-ray exposures, and scoliosis treatment. Location information would also be obtained. Patient tracing will be conducted through resources at both NCI and the support services contractor. In the feasibility study, about 35 percent of the tracing was conducted through NCI resources and 65 percent by the support services contractor. Once a person has been located, a questionnaire would be mailed and would include information on medical history, family history of breast cancer, any diagnoses of tumors, nutritional factors, and reproductive factors (e.g., age at first pregnancy, menstrual factors, and ages at menarche and menopause). Death certificates would be collected for all decedents. When a malignant neoplasm is identified from the certificate or questionnaire, hospital discharge summary sheets and pathology or surgery reports would be requested. If an autopsy were performed, request for a copy of the autopsy report would be made. Because scoliosis has been reported to be common in some cancer prone disorders (such as ataxia telangiectasia and neurofibromatosis), information on these conditions will be abstracted or obtained when available.

A special one page questionnaire, similar to that used in the feasibility study, would be sent to hospitals of treatment for all reported breast tumors or biopsies, leukemias, and cancers of the lung and thyroid. Radiation dose estimates would be based on information contained in the patient medical record and the data from the x-ray films and machine parameters. These estimates would be developed under another contract.

Expected numbers of deaths and breast cancer incident cases would be calculated by applying relevant age, sex, race and calendar specific rates (from U.S. vital statistics and SEER data) to the appropriate woman years at risk. The observed number of cases would be compared with that expected to determine if a significant excess exists. Tests for trends in risk as a function of radiation dose would be conducted. The key points of the analysis are the effect of age at exposure on risk; whether or not stage of breast development at exposure is an important determinant of risk; the relationship between total absorbed dose, dose fractionation, age at exposure, and tumor latency; and the relationships between various other host factors and radiation dose on the expression of tumor risk. Other cancers would be similarly evaluated.

Based on the results of the feasibility study, apprximately 100 breast cancers would be identified in the proposed study. A sample size of 8,500 women would be sufficient to detect a relative risk of breast

cancer of 1.8 with 99 percent power. If the relative risk were 1.4 the associated statistical power for a sample size of 8,500 women would be 80 percent.

Contracts approved for recompetition:

Epidemiologic surveys of human retroviruses. Recompetition of a contract held by Medical Research Council, London. Five years, estimated cost $300,000 per year.

The Epidemiology & Biostatistics Program has been active since 1981 in elucidating the epidemiology of human retroviruses with a particular focus on the relationship to human cancer. With the rapid pace of discoveries in this field and the recognition tht these agents are often more common in overseas locales, a contract was established in 1985 to provide a flexible and rapid mechanism for undertaking internationally based studies of human retroviruses.

When the concept for this project was first approved in 1983, the focus was on undertaking surveys of leukemia/lymphoma for HTLV-1 in various geographic areas. However, with the emergence of AIDS in Africa and the recognition that new types of human retroviruses may be detected through cross reactions with known retroviruses, the scope of activities were expanded with the award of this contract in 1985 to explore retrovirus-cancer relationships from a broader perspective. Nonetheless, the basic approach for conducting these surveys has remained the same. The principal investigator has the responsibility of providing liaison for establishing surveys in various regions to explore specific etiologic hypotheses. Protocols are developed by NCI, the PI and local collaborators for conducting the epidemiologic surveys. Subcontracts are written to cover the costs necessary for sample and data collection including T and B cell typing of leukemia/lymphoma where applicable. Three major types of studies have been undertaken: surveys of leukemias and lymphomas for HTLV-1; studies of HTLV-3 in relationship to AIDS and cancer, particularly for Africa; and sample collection for isolation of human retroviruses, including new variants suspected on the basis of serologic testing.

The current contract provides a flexible and responsive mechanism for surveys of human retroviruses in cancer and AIDS. Project sites are targeted by NCI and the PI to examine specific questions. Study sites are selected on the basis of new data and are done in collaboration with local scientists who have access to study populations. After suitable discussions, the PI travels to the potential study sites to explore project feasibility and local circumstances which might influence research design. After initial on site assessment, a protocol is developed involving NCI, the PI and local collaborators. Protocol review is undertaken at NCI by the TEP Review Committee and on site by local institutional review boards, with particular emphasis on meeting NIH human subject guidelines. A subcontract is then established by the PI to provide funding and clear delineation of how data and samples are to be collected. The PI periodically visits the project sites to ensure that expected deliverables are being collected appropriately. Samples and data are shipped to NCI for further analysis. Laboratory testing is performed at the newly establed Human Retrovirus Epidemiology Laboratory at Frederick Cancer Research Center, with selected virus isolation work performed in the laboratory of Robert Gallo. Based on results, extensions of the investigator may be undertaken.

Future Directions: HTLV-1 and leukemia/lymphoma. A continued focus of this project is to support surveys in selected geographic locales to define the distribution of HTLV-1 and its associated diseases. Targets for investigation will be chosen based on clues arising from clinical observation and/or results of serologic surveys of normal populations. In addition to the sites currently under study, new research initiatives are being considered in other areas as well, including some with foci of myelopathy associated with HTLV-1 infection. The work jn Nigeria and recent reports from southern Italy also suggest that retroviruses closely related to HTLV-1 may be linked to lymphoma. Surveys to explore these relationships may be undertaken depending upon the availability of serologic tools for detecting these new variants.

HTLV-3 and AIDS. Continued efforts will be made to define the relationship of HTLV-3 infection and the risk of various cancers, with specific future directions dependent on the results of current studies. For example, we plan to explore the hypothesis that HTLV-3 associated immunodeficiency amplifies the risk of cancer, particularly of types with a known or suspected link to DNA viruses (e.g., cervical cancer).

New retroviruses. Current sutdies in Tanzania and Nigeria, based on preliminary data, should help to isolate new retroviruses that may be causes or cofactors in certain cancers. Future approaches will depend upon the nature and timing of virus isolations and the development of reagents suitable for seroepidemiologic study. Ongoing efforts are focused on developing and maintaining mechanisms for prospective surveys of selected populations.

In summary, current initiatives will be continued with suitable expansion based on results of ongoing projects. The contract is designed to provide a flexible mechanism for pursuing new leads in a timely and rapid manner. Thus, some work to be performed under this contract in future years is purposefully not yet defined, based on our assessment that the rapid pace of discoveries and events in this field will require multidisciplinary approaches that respond to unexpected observations, opportunities and advances in knowledge.

Record linkage studies utilizing resources in population based tumor registries. Recompetition of master agreement contracts currently held by 25 registries. Estimated cost of the new master agreements over four years is $1.8 million.

Population based cancer registries provide unique opportunities to conduct record linkage and feasibility studies of cancer etiology. The registries typically obtain detailed information on cancer diagnosis and treatment on individual cancer patients. Occasionally, there also exist rosters of individuals, characterized by medical conditions, occupations, use of pharmaceuticals, or other environmental exposures, which can be linked to the cancer registry files to generate or test etiologic hypotheses. Populations exposed to various biological agents or for whom biological specimens have been obtained can also be matched against cancer registries. There has been considerable enthusiasm for record linkage studies in recent years for pragmatic reasons because they avoid problems associated with response rate or informed consent. However, such studies have not been pursued to a great degree, and this project has been an attempt to stimulate research in this area.

In 1983 the Board of Scientific Counselors approved the concept to conduct studies utilizing resources in population based tumor registries. In March 1985, 22 registries were awarded master agreements, with three more added to the pool of qualified sources in early 1987. The first master agreement order for a particular record linkage project was made in September, 1985. The concept approval expires in March 1988 so the request for a recompetition must be made now. The initial experience has proved that this mechanism is a cost effective way to conduct, as well as to encourage, collaborative research using record linkage

approaches in population based registries. Large scale epidemiologic studies are not being conducted; in most cases, small cost efficient investigations have been initiated. If the results from the initial investigations are provocative, they might then graduate to larger, more analytic investigations requiring separate concept review and funding.

Ten master agreement order RFPs have been issued and 10 individual awards have been made. The average amount of each award has been approximately $50,000, and only $442,000 to date has been committed to the investigations. This program wide project has taken a few years to get off the ground, but it now appears to be running efficiently.

Preliminary results from several of the early studies are noteworthy. Rosters of over 8,900 epileptics have been linked to the Danish Cancer Registry, and 419 cancers identified. Significant excesses have occurred for cancers of the liver, brain and nervous system. Significantly decreased risks of cancers of the uterine cervix and ovary were also observed. Possible explanations for these associations (including an altered cancer risk due to epilepsy or an underlying disease, radiation emitting thorotrast used during cerebral angiography, or to anticonvulsive drugs such as phenobarbital and hydantoin) are being pursued through review of existing medical and treatment records. In addition, the risk of cancer in approximately 4,000 children of the epileptics will be evaluated. Additional tracing and linkage with registry records of the epileptics and their children are continuing.

In a study of leukemia following adjuvant chemotherapy for breast cancer, four MAOs have been awarded to U.S. registries. Initial record linkage has identified over 100 secondary leukemias and preleukemias among breast cancer patients and ongoing reserch is now being conducted to clarify the component of excess leukemias related to specific chemotherapeutic agents and/or radiotherapy and to evaluate dose response. Over 1,200 women in Israel who received radiation to the ovaries and/or pituitary gland for infertility in the 1940s are being evaluated for cancer incidence using resources of the Israel Cancer Registry. In addition, rosters of approximately 1,000 Israeli children who underwent intense chest fluoroscopies during heart catheterization procedures are being linked to cancer registry records to determine whether an increase in cancer risk due to radiation exposure can be detected. In Shanghai, census data on occupation are being linked to cancer registry data to generate clues to workplace risk factors. In Sweden and Denmark, computerized files on individuals prescribed various drugs are being matched with the cancer files to assess cancer risks associated with estrogen-progestin combination therapy. In Denmark, over 4,000 cases of brain cancer and 2,000 cases of multiple myeloma have been identified for a case control study of occupation and cancer. Industrial hygienists are evaluating exposures in jobs held by these subjects for which computerized records are available. These investigations indicate the wide range of hypotheses, from cancer treatment to occupational exposures, that can efficiently be studied using this master agreement mechanism.

This program wide project provides managerial, data collection, and computer processing support to address issues where resources from population based tumor registries could be best utilized. The services are used for collaborative research, including support of investigators in the SEER program and other population based registries. For cohort studies, rosters of study subjects are linked to cancer registry records, new cancers are identified and compared to expected values on the basis of rates in the general population applied to the appropriate person years at risk. For case control studies, cancer cases are identified and appropriate controls selected and additional detailed exposure and risk factor information is obtained from additional sources, such as the hospital of treatment. The contracts are in the form of master agreements. Recipients compete for awards after a master agreement order RFP has been issued. Currently, 25 national and international cancer registries have received master agreement awards.

Because of the large number of cancers reported to population based registries, small effects or rare cancers can be effectively studied by combining results from several registries. In addition, since existing records are already computerized, record linkage studies can usually be conducted efficiently. Additional studies to be considered uder this project include: (1) specific studies linking population rosters (such as the linkage of twin registries and cancer registries to evaluate childhood cancer in twins following prenatal x-ray); (2) further linkage of occupational rosters and cancer registries to test and generate hypotheses regarding occupational cancer; (3) linkage of state unemployment insurance files or other special state occupational rosters with the appropriate U.S. cancer registries; (4) further linkage of data of several cancer registries to evaluate the influence of radiation treatment on the likelihood of second cancers (such as the risk of leukemia following radiotherapy for endometrial cancer); (5) linkage of data in several cancer registries to evaluate leukemia risk following chemotherapy (such as for testicular cancer or small cell carcinoma of the lung); (6) the linkage of tuberculosis records with cancer registry records to identify excess malignancies, especially lung cancer; (7) linkage of rosters of patients treated for various diseases with all participating U.S. cancer registries in order to locate and identify cancers (such as for existing rosters of patients receiving renal transplants and dialysis; (8) linkage of genetic and congenital disease registries to evaluate associations with subsequent cancer development; and (9) linkage of serum banks with cancer registry records.

It is planned that feasibility studies, generally at minimal expense, would be initiated to determine whether appropriate records can be linked and to evaluate the type and quality of additional data that can be abstracted from existing files. These might then be followed by enhanced studies to obtain additional information available from hospital and other records.

Cell culture identification and cytologic/karyotypic analysis. Recompetition of a contract held by Children's Hospitala of Michigan. Estimated cost is $2,277,325 over five years.

The study of cultured tumor cells of human and animal origin is fundamental to understanding the relationship of viruses to the processes by which tumor formation is initiated or promoted. Many experimental techniques in virology, immunology, cell biology, and biochemistry require the precise duplication of cells or mixtures of cells, by different investigators with the result that cell identification services are of great importance. The extensive use and informal cross supply of cell cultures among investigators has resulted in a major problem of frequent erroneous or mislabeled cell lines. Correctly identified cell lines are of critical importance since research utilizing misidentified cell lines is a waste of time and research funds.

This project is a resource effort for the inter and intraspecies identification of cells in culture. In this effort three basic techniques or combinations of them are used: isoenzyme analysis, immunofluorescent testing, and cytogenetic and karyotypic analysis. Over

the past 14 years, more than 3,600 cultures have been examined or tested, and over the past year approximately 300 cultures have been submitted for examination and testing. In the current contract period, the number of cultures submitted is approximately 50 percent above that received in the previous contract period. The need for proper cell culture identification remains high, since over 20 percent of the cell lines submitted for cell identification have been discordant with the presumed identity. Approximiately this same level of cell species discrepancy has persisted throughout the duration of the effort.

This work benefits the cancer research community by providing investigators with verification of identity of cell lines; applying uniform standards of quality control; cost savings by minimizing the duplication of effort at numerous laboratories; and comparability of results from different laboratories since the same species or type of cell lines are used. This contract received approximately $50,000 in cost reimbursement (payback) receipts in FY 1985 and it is estimated that $60,000 will be received for FY 1986 and $70-80,000 in FY 1987. It is apparent that interest in this service is increasing in the scientific community.

In the last six months, a need for a more extensive cytology/karyology service has become apparent as a result of the increased emphasis on chromosomal translocations in malignancy and the possible role of such translocations in amplification of oncogenes or in inappropriate overexpression of normal cellular proteins. More details are also being requested in terms of normal chromosome distribution, and specific identification of chromosomal breaks or translocations. These requests involve more karyotypic analysis, and investigators are also submitting multiple cell lines to assure that the same cell type is maintained throughout an experimental protocol. These factors have resulted in additional effort in the cytogenetics area without any concomitant decrease in other areas. The need for an additional cytogeneticist to carry out these procedures and the purchase of necessary microscopic equipment and supplies for the project account in large part for the cost increases associated with this concept. However, we plan to increase the fee charged for this more detailed service in order to recoup the majority of the costs associated with it. We also anticipate that as in the past a significant portion of the costs will be borne by those utilizing either the basic identification service or the more detailed karyology service which we propose to offer.

Since it is not physically possible or economically feasible for all laboratories using tissue or cell cultures to have expert inhouse capability to identify cell lines in use, and since 20-25 percent of the lines submitted for identification are not what the submitting laboratories presumed them to be, there is a need to continue this service.

John Cole, project officer, noted that about 60 percent of the recipients of the cell identification services are either government investigators or grantees--39.7 percent intramural NIH, 9.6 percent other government, and 9.1 percent grantees. The 40 percent going to extramural investigators includes 7.5 percent to universities and hospitals, 13.2 percent to ATCC, and 20.9 percent to commercial organizations.

In response to Board member George Vande Woude's question on why there is such a big difference between the cost of the service and the payback fees received, Cole said, "We feel this very important service should be made available to as many as possible. We don't want to price it out of range."

Board chairman Barry Pierce read a letter from member William Benedict, who did not attend the meeting, in which Benedict objected to immediate approval of the concept. But Board ' member Hilary Koprowski said "this is a very useful service which we don't want to interrupt," and moved for approval. The Board went along unanimously.

The Board also approved without dissent a two year extension of the contract with M.D. Anderson for dosimetry studies, for a total estimated cost of $195,000. The existing five year contract will expire in 1988.

The Board rejected recompetition of the contract with Biomedical Research Institute for cell culture support services for the Laboratory of Cellular & Molecular Biology. This provided for cleaning and preparation of glassware by immersion in steam heated kettles of concentrated acid, a procedure a Board site visit team three years ago said was unnecessary.

Project officer Katherine Sanford said the reviewers did not hear the justification for the contract, and insisted that "if you disapprove this contract, you are disapproving our work," which is the identifying and characterizing stages in malignant neoplastic transformation with emphasis on human epithelial cells in culture. Board members suggested that other investigators do similar work with more modern methods and they voted 13-0 to against the concept, with two abstentions.

RFPs Available

Requests for proposals described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs, citing the RFP number, to the individual named, the Blair building room number shown, National Cancer Institute, NIH, Bethesda MD 20892. Proposals may be hand delivered to the Blair building, 8300 Colesville Rd., Silver Spring MD, but the U.S. Postal Service will not deliver there. RFP announcements from other agencies will include the complete mailing address at the end of each.

RFP NCI-CN-75404-34

Title: Support contract for special populations initiatives

Deadline: April 20

NCI is soliciting proposals from small business organizations interested in providing all necessary personnel, facilities, equipment, materials and supplies, except as may otherwise be provided by the government, for research and logistical support to the Special Populations Studies Branch in the conduct of planning, data management and analysis, scientific review, report and article preparation, administrative support and liaison within the Div. of Cancer Prevention & Control.

This procurement is a 100 percent set aside for small business. For the purpose of this procurement, a small business is so classified if its average annual receipts for the preceding three fiscal years do not exceed $3.5 million.

Contract Specialist: Elizabeth Abbott
RCB Blair Bldg Rm 2A01
301-427-8745

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