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Wyngaarden Recommendation On New Director Due Nov. 10; Five NCI Staff Members Nominated

The NCI director search committee chaired by NIH Director James Wyngaarden, with a Nov. 10 deadline to submit its recommendations to the White House, reportedly has had an enthusiastic response to Wyngaarden's wide open invitation to

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In Brief

Relocation of NCI Offices Nearly Complete; Hungary's Eckhardt UICC President Elect

RELOCATION of NCI offices from the Landow, Blair and Westwood buildings into the Executive Plaza Building in Rockville, MD, will be completed by mid-November. The Div. of Cancer Prevention & Control and Research Contracts Branch offices in Blair had all been moved by the end of last week. Since those were in a different telephone exchange, in Silver Spring, than those in the Bethesda locations, they all have new phone numbers. For the present, dial the old numbers (with the 427 prefix), and an NIH operator will provide the new number. The Div. of Extramural Activities offices in Westwood should be moved by the end of next week. They will retain their phone numbers, as did the Div. of Cancer Etiology and Div. of Cancer Treatment offices moved earlier this year from Landow. . . . **SANDOR ECKHARDT** of Hungary has been elected president elect of the International Union Against Cancer (UICC). He will take office at the 15th International Cancer Congress in Hamburg in 1990. Gerald Murphy of the U.S. was reelected secretary general; Max Burge of Switzerland was elected treasurer; Charles Ebersole of the U.S. was elected finance chairman; and Kay Horsch of the U.S. was elected public education chairman. . . . **ELIZABETH WEISBURGER**, assistant director for chemical carcinogenesis of NCI's Div. of Cancer Etiology, will retire in December after 39 years with the Institute. Among the many honors she has received as one of the leading scientists in her field is the Public Health Service Distinguished Service Medal, the highest PHS award. The DCE Board of Scientific Counselors gave her a standing ovation when Director Richard Adamson announced her retirement last week. . . . **BARUCH BLUMBERG**, vice president for population oncology at Fox Chase Cancer Center and winner of the 1976 Nobel Prize in medicine, received the John P. McGovern Award from the American Medical Writers Assn. for his role in communicating science to the public.

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Five NCI Staff Members Nominated; Center Directors Dominate Outside List

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nominate candidates for the position vacated by Vincent DeVita Sept. 1. Dozens of names have been received as the result of a letter Wyngaarden sent, "at least 1,000 letters," he said, inviting recommendations.

Wyngaarden's committee includes Assistant Secretary for Health Robert Windom and two Dept. of Health & Human Services personnel officials. It also includes as nongovernment advisors Paul Marks, president of Memorial Sloan-Kettering Cancer Center, and Benno Schmidt, chairman of the MSK Board.

Schmidt was the first chairman of the President's Cancer Panel, and his recommendation of Frank Rauscher for NCI director was accepted in 1972 by President Nixon. At that time, the National Cancer Act required the Panel to make the recommendation to the President, but that provision was dropped in one of the renewals of the Act.

That would not prevent the present Chairman, Armand Hammer, and his fellow Panel members, John Montgomery and William Longmire, from coming up with their own recommendation, however. They could go through Wyngaarden's committee or they could send it directly to the White House.

The Cancer Letter previously had learned through a White House source that the search committee's recommendations would be considered, along with candidates nominated by others. Some candidates possibly will be on both lists.

The source also indicated that present NCI staff members would not be considered. Wyngaarden, in his letter soliciting recommendations, had no such restriction, and at least five current staff members have been nominated:

* Alan Rabson, who is enjoying his role as acting director, and staff members are enjoying working with him. He is the most senior member of the NCI Executive Committee, having served as director of the Div. of Cancer Biology & Diagnosis since 1975.

* Bruce Chabner, director of the Div. of Cancer Treatment since 1981. A nationally recognized scientist, he has proven his administrative capabilities in running DCT. "I'm enjoying what I'm doing now, but if it happens, it happens," he said last week.

* Richard Adamson, director of the Div. of Cancer Etiology since 1981. A no-nonsense administrator, he is a passionate defender of the National Cancer Act and has clashed with Wyngaarden over its interpretation. He probably will not be on the list Wyngaarden sends to the President, but may well be on the list generated by the White House.

* Robert Wittes, presently DCT acting deputy director, former director of the Cancer Therapy Evaluation Program and for the moment still editor of the "Journal of NCI." He plans to leave the government in December to join Bristol-Myers as senior vice president for cancer research. His creative and articulate approach to clinical trials and patient accrual problems has won acclaim within NCI and among the cooperative groups.

* John Minna, chief of the NCI-Navy Medical Oncology Branch. Like Robert Young and Marc Lippmann, Minna is ready to move either up or out, and has turned down at least one cancer center directorship. His scientific credentials are unmatched.

There are undoubtedly other NCI staff members who have been nominated, chief among them Peter Greenwald, director of the Div. of Cancer Prevention & Control; Steven Rosenberg, chief of DCT's Surgical Oncology Branch; Samuel Broder, director of DCT's Clinical Oncology Program; and Robert Gallo, chief of DCE's Laboratory of Tumor Cell Biology. **The Cancer Letter** was unable to confirm those nominations, however.

The list of those outside the government who have been nominated is dominated by cancer center directors.

They include Alan Sartorelli, director of the Yale Comprehensive Cancer Center; Charles LeMaistre, director of the Univ. of Texas M.D. Anderson Cancer Center; Bernard Weinstein, director of Columbia Univ. Comprehensive Cancer Center; and Richard Steckel, director of the UCLA Jonnson Comprehensive Cancer Center. David Korn, dean of the Stanford Univ. School of Medicine and chairman of the National Cancer Advisory Board, has also been nominated.

Some of those, and perhaps all of them, may have removed themselves from consideration. Giving up a prestigious, secure position for another prestigious job but with no guarantees, while taking a healthy cut in pay, may not appeal to some.

Although the White House asked for Wyngaarden's list by Nov. 10, no date has been set for announcing the final selection. Indications are that will be before the end of the year.

Construction, Senior Biomedical Research Service Not In Legislation

President Reagan had not revealed by **The Cancer Letter**'s press time this week whether he would sign S. 2889, the Health Omnibus Extension Act of 1988, which includes renewal of the National Cancer Act and reauthorization of various other NIH programs.

The President has until Nov. 5 to sign the measure. Since the 100th Congress has adjourned, if he does not sign it, that would constitute a "pocket veto." Congress would thus have no opportunity to override. If he vetoes it, the new Congress then could vote on an override motion.

When a President fails to sign a bill within 10 days while Congress is in session, it becomes law without his signature, but a pocket veto kills it.

The bill includes a provision establishing a new National Institute on Deafness and Other Communication Disorders. President Reagan, who at first had opposed creating another institute at NIH, has more recently indicated he supports it. It does not appear that there are any other provisions in the bill which would trigger a veto.

Two provisions which the Administration did oppose were eliminated: providing NIH wide construction grant authority, which was in the bill authored by Sen. Edward Kennedy which passed the Senate; and establishment of a Senior Biomedical Research Service, which was removed from the Kennedy bill before the Senate vote.

The new construction grant authority was taken out by House-Senate conferees. It would have left in place NCI's separate construction grant authority (which has been unfunded for two years).

The Senior Biomedical Research Service was Kennedy's response to the need to provide incentives for top government scientists to stay on the job. It would have permitted pay increases of 10-15 percent over top Public Health Service and civil service levels.

So two of the most vexing problems facing the biomedical research community and NIH remain unaddressed in the new legislation. Upgrading and expanding research facilities will have to be one of the critical issues in the next reauthorization, which will come in two years instead of the usual three. S. 2889 is only a two year authorization.

The problem of retaining key scientists at NIH may never be solved entirely, although a pay increase would help. The next round of hearings by the House and Senate authorizing committees probably will focus on that issue along with research facilities.

Further analysis of the bill passed in the final hours before Congress adjourned turned up the following amendments which were requested by NCI, the National Cancer Advisory Board, and other cancer program advocates:

--Ex officio members of the NCAB and other NIH advisory councils are nonvoting members (the previous reauthorization inadvertently had given them voting status).

--All advisory councils, including the NCAB, must have at least two members who are experts in public health and social sciences. The NCAB presently meets that requirement.

--NIH nurses and allied health personnel must be paid at the same levels as their counterparts in Veterans Administration hospitals. That requirement was included in legislation two years ago for nurses, but allied health personnel were left out. VA pay has been higher than NIH's.

--NCI was granted the same flexibility as the National Science Foundation in determining whether the Government Printing Office or a contract printer is used for any particular publication.

NCI's public, patient and physician information programs were broadened to include "information that will help individuals take personal steps to reduce their risk of cancer, to make them aware of early detection techniques and to motivate appropriate utilization of those techniques, to help individuals deal with cancer if it strikes, and to provide information to improve long term survival."

Also, to "continue and expand programs to provide physicians and the public with state of the art information on the treatment of particular forms of cancers, and to identify those clinical trials that might benefit patients while advancing knowledge of cancer treatment; to assess the incorporation of of state of the art cancer treatments into clinical practice and the extent to which cancer patients receive such treatments; to maintain and operate the International Cancer Research Data Bank which shall collect, catalog, store and disseminate the results of cancer research and treatment undertaken in any country for the use of any person involved in cancer research and treatment in any country; and to utilize information systems available to the public."

DCE Board Approves Concepts For 14-19 New Grants, Four RFPs

Three new grant supported research projects with first year funding estimated at $2.6 million received concept approval last week from the Div. of Cancer Etiology Board of Scientific Counselors.

The new projects, which will result in an estimated 14 to 19 grants, are for new approaches to studying Epstein-Barr virus oncogenesis; studies of mechanisms of protease inhibitor anticarcinogenesis; and studies of mechanisms of multistage carcinogenesis in the prostate.

The Board also gave concept approval to four new competitive contract supported projects, including a three year, $750,000 per year case control study of cutaneous malignant melamona and a new $1.2 million a year support contract, and to five noncompetitive new and renewal contracts.

A new initiative for procurement of purified viral proteins, synthetic peptides and oligonucleotides, and monoclonal and polyclonal antibodies received concept approval. This will be an RFP, with the contract to be supported with DCE's allocation of AIDS funds. Details of this concept will be reported in the Nov. 14 issue of **AIDS update.**

Concept statements follow:

New approaches to studying Epstein-Barr virus oncogenesis. A total of $850,000 will be set aside for first year funding, which is expected to fund four to five grants, each for five years.

Epstein-Barr virus has been associated with several neoplasias, including Burkitt's lymphoma and nasopharyngeal carcinoma and with several infectious diseases, including infectious mononucleosis and severe chronic infectious mononucleosis. Recent evidence appears to link EBV with parotid gland tumors and B-cell lymphomas in immunosuppressed individuals, particularly AIDS patients. In vivo studies of EBV oncogenesis are complicated by the long interval between primary infection and the occurrence of neoplasia; and by the high prevalence of EBV infection in geographic areas where a high frequency of EBV associated neoplasias occurs: E.g., in the malaria belt in Africa in the case of Burkitt's lymphoma and in the Far East in the case of nasopharyngeal carcinoma.

In vitro studies of EBV have been hampered by the lack of a lytic infection system. Studies have focused on lymphocytes which have been immortalized/transformed by EBV infection and in which a limited set of viral gene products is expressed. The application of recombinant DNA technology to this system has led to progress in elucidating the structure of the viral genome, further definition of viral gene products, and identification of several regulatory regions of the viral genome. Additionally, both B-cells and epithelial cells appear to be sites of viral latency and replication. However, the viral and host factors determining the disease manifestations and clinical outcomes for EBV infections are, as yet, undefined.

While a number of investigators are intensively studying specific aspects of EBV replication and tumorigenesis, few if any are directly examining the specific issue of the interaction of viral and host factors which may determine the outcome of individual EBV infections.

A workshop held earlier this year, cochaired by DCE Board member Myron Essex and George Miller of the National Institute of Allergy & Infectious Diseases, identified a number of issues in EBV oncogenesis in which knowledge is limited and which require more active investigation (Essex summarized the workshop findings in a report to the Board at last week's meeting). For example, EBV has been associated with both lymphoid and epithelial neoplasias. Within an individual, it is not clear whether there are two separate reservoirs of EBV latency, one epithelial and one lymphoid, or whether there is continuous infection and transofrmation of B-cells from an epithelial reservoir. The viral and host factors which normally prevent the progression from latent infection to neoplasia and the viral gene products which are involved in the oncogenic process have not been defined. Experiments to approach these issues are technically difficult and are limited by a number of factors including the lack of a lytic replication system, the lack of mutants, the lack of animal models, limited quantities of human tissues, limited availability of gene product specific reagents such as monoclonal antibodies, and limitation of methodologies currently available to detect viral gene products present in low quantities or in small percentage of cells. Thus, new approaches to address these fundamental issues of EBV oncogenesis are needed.

The overall thrust of this RFA is to stimulate research on the mechanisms of EBV oncogenesis by developing and using new methodological approaches to overcome the difficulties inherent in EBV research. Examples of research objectives would include (1) use of novel methods and probes to define RNA transcripts unique to or with clinical significance for different EBV neoplasias; (2) use of new approaches to alter (mutate) the viral genome followed by the study of the effect of altered genes on viral oncogenesis; (3) use of cell lines expressing individual EBV gene products (both structural and regulatory) to define viral genes and assess their role in the neoplastic process; (4) use of specific reagents such as monoclonal antibodies to viral gene products to determine the role of regulatory and structural EBV proteins in the neoplastic process; (5) measurement of host response to individual viral proteins with the goal of delineating differences in the host response in specific EBV associated neoplasias; (6) delineation of differences in cell mediated responses in individuals with different EBV neoplasias; and (7) exploitation of EBV's unique pathologic aspects, such as the use of the CR-2 receptor and the activation of B-cells during the infectious process, to develop approaches to alter these unique aspects of EBV pathogenesis with the ultimate aim of preventing or reversing neoplastic conversion.

Furthermore, in studies involving differences between various EBV associated neoplasias, investigators should consider not only the classical EBV associated neoplasias such as Burkitt's lymphoma and nasopharyngeal carcinoma, but also give some emphasis to newer EBV related neoplasias such as EBV lymphomas in immunocompromised individuals, EBV tumors in other areas of the oropharynx such as the parotid gland, and other new EBV associated diseases such as hairy leukoplakia.

Board member George Vande Woude asked if the RFA is expected to stimulate participation in this research by new investigators or is aimed at those experienced in the field. "This is a very complicated area," he said.

"We hope to get some new investigators involved, along with some experienced," Susan Spring, the DCE program director for the project, said. ""We also hope for some collaborations."

Mechanisms of protease inhibitor anticarcinogenesis. First year funding was estimated at $750,000 which would support from four to six grants, each for five years.

Evidence has accumulated that protease inhibitors can suppress both transformation in culture and tumorigenesis in animals. Transformation suppression has been shown in several different in vitro systems employing a variety of inducing agents such as x-rays and UV light, polycyclic aromatic hydrocarbons, 4-nitroquinoline oxide, beta propiolactone, N-methyl-N'-nitro-N-nitrosoguanidine, and steroid hormones. Some interpret these results to mean that different carcinogens induce similar carcinogenic processes involving at least one critical cellular proteolytic enzyme which is susceptible to protease inhibitor suppression. Among the inhibitors effective in vitro have been the small peptide microbially derived inhibitors (for example, the endopeptidases lelupeptin, antipain, and chymostatin), large polypeptide vegetable derived inhibitors (for example, Bowman-Birk inhibitor, chick pea chymotrypsin inhibitor, potato chymotrypsin inhibitor-1) and small, chemically synthesized compounds (tosyl-phenylalanine-chloromethylketone [TPCK] and tosyl-L-lysine-Chloromethylketone [TLCK]).

Some evidence exists that protease inhibitors which inhibit the protease chymotrypsin are the most effective in suppression of malignant transformation. It is noteworthy that treatment of cells in culture with low concentrations of some protease inhibitors has an irreversible inhibitory effect on the transformation process, even when added to cultures for short time periods; and that transformation inhibition is still observable when the inhibitor is added to the cultures long after carcinogen exposure.

In vivo studies also have shown or suggested that several types of protease inhibitors can suppress tumorigenesis in animals induced by a variety of carcinogens, in a number of organ systems, and in several species. These studies include suppression of two stage skin papilloma formation and carcinogenesis in mice (TLCK, TPCK, leupeptin, and soybean diets rich in protease inhibitors), dimethylhydrazine induced mouse colon tumorigenesis (epsilon-aminocaproic acid, leupeptin and a crude extract of BBI), x-ray and chemically induced breast cancer in rats (soybean diets, leupeptin), and dimethylbenzanthracene induced cheek pouch carcinomas in hamsters (soybean extract enriched in BBI), and genetically determined, spontaneous hepatocellular carcinomas in inbred, C3H mice (soy protein concentrate).

Epidemiolcgic data from a number of population studies have shown that vegetarians and populations consuming large amounts of vegetables have lower tumor risks for a number of organ sites. Many vegetables contain protease inhibitors which could contribute to the lowered incidences observed. A new study on Seventh Day Adventist populations indicates that high legume consumption (such as beans, peas and lentils) and dried fruit is associated with highly protective relationships to pancreatic cancer risk. Legumes are a known rich source of protease inhibitors.

A workshop held last December, chaired by DCE Board member Dietrich Hoffmann and by Lee Wattenberg concluded that six major areas of research and development were necessary to further define the usefulness of protease inhibitors as potential human cancer preventive agents (Hoffmann summarized the workshop recommendations at last week's meeting):

1. Research and development on sources of protease inhibitors and means of expediting their availability to the scientific community in both small and large quantities in defined states of content and purity.

2. Analysis of human foods, including development of appropriate methodology where necessary, for protease inhibitor content.

3. Reevaluation of epidemiological data regarding cancer occurrence in relation to known protease inhibitor content and characteristics in human foods.

4. Greatly expanded animal studies on efficacy of protease inhibitors in cancer prevention; studies should include among other things target organ definition, many more types of protease inhibitors, and dose response characteristics in prevention.

5. Investigations on potential adverse side effects of protease inhibitors, with studies from the whole animal to the molecular level, including investigations on possible effects of anticarcinogenesis/antitransforming protease inhibitors on critical protease activities essential for normal physiological processes.

6. Greatly expanded studies on mechanisms of anticarcinogenesis of protease inhibitors.

DCE staff envisioned that these recommendations can be implemented by a variety of initiatives. Recommendations five and six form the basis for this concept for an RFA.

Research funded under this RFA would emphasize basic studies on the mechanisms of protease inhibitor anticarcinogenesis. The intended research would encompass both in vitro and in vivo systems, and would be confined to investigations employing known, well characterized models of carcinogenesis. Examples of studies (by no means inclusive) are (1) investigations on the identification and characterization of the target molecules significant to the anticarcinogenic action of protease inhibitors; (2) studies on protease inhibitor suppression of oncogene expression in appropriate model systems; (3) investigations on the role of protease inhibitors in suppression of activated oxygen species employing model systems of significance to anticarcinogenesis; and (4) possible preventive interactions, as well as possible side effect producing interactions, of protease inhibitors directly or indirectly with host immune or endocrinological systems, including possible interactions with autocrine or paracrine systems of control involving growth factors.

Carl Smith is the program director.

Mechanisms of multistage carcinogenesis in the prostate. First year funding is estimated to total $1 million, which would support six to eight grants of five years each.

The incidence of prostate cancer has been steadily increasing since 1937 to the point where today it is the second leading cause of cancer related deaths in the American male population (third if colon and rectal cancer is combined). It has been predicted that 99,000 U.S. men will be diagnosed with prostatic cancer in 1988 and over 28,000 will die of this disease. These figures are projected to become increasingly dismal in the future because of the rising life expectancy of the American male population and the fact that late in life no other form of cancer increases in incidence with age as rapidly as does prostate cancer. Thus, research focused on delineating the cellular and molecular mechanisms underlying the transformation and progression of prostatic epithelial cells is urgently needed.

Compared to other forms of cancer there is very little information available either on the causes of prostatic cancer or the mechanisms by which normal prostate epithelial cells develop and progress to latent and invasive cancer. Emphasis has traditionally been placed on a probable role of androgenic hormones, because it is known from animal studies that normal prostatic epithelial cell growth is regulated by these hormones and prostate cancer is not found in males castrated before puberty.

Other studies, however, have made it clear that environmental influences are also of major importance. Epidemiological studies have demonstrated that the rate in Japan (4.3/100,000) is much lower than in the U.S. (61/100,000). However, the incidence of prostatic cancer

in first and second generation Japanese men who have migrated to the U.S. is similar to that of the American male population.

Histopathological examinations at autopsy of the prostates of men whose deaths were due to causes other than cancer have revealed that the pattern of prostate premalignancy is different from that seen in other tissues. What has been found repeatedly is that regardless of national or geographic locale, by age 50 approximately 30% of all men have histologically detectable latent prostate cancer. In contrast, only about 4% of American men over age 45 will eventually develop clinically diagnosed prostate cancer compared to a much smaller proportion among Japanese men. The reason for wide geographic variations in the rate of progression from latent to invasive cancer is unknown, but it seems likely that environmental and lifestyle factors play a significant role and need to be delineated.

Although prostate cancer is a major medical problem, recent analyses have revealed that very few investigators are currently focusing their studies on prostatic epithelial cell carcinogenesis. Another problem impeding progress in understanding the cause and prevention of prostatic cancer is a lack of information about the specific cell types involved in neoplastic transformation and their lineages. A third major problem is the absence of a reliable, confirmed animal model for studying carcinogenesis of the prostate gland. This is in marked contrast to other sites of solid tumors in humans for which there are models for carcinogenesis studies. Further, in contrast to most of the other forms of human cancer, there is very little information on the ability of the various types of prostatic cells, both within and between different population groups, to metabolize suspected environmental carcinogens. Finally, the roles played by hormones and diet in initiation and progression of the disease remain unclear.

Purpose of this initiative is to provide a means to enhance and expand multidisciplinary investigations on the mechanisms of multistage carcinogenesis in animal and human prostatic epithelial cells through the issuance of an RFA for principal investigator initiated research grants.

New advances in prostate tissue and cell culture and descriptions of potentially useful (but not yet confirmed) animal models have been published. In addition, molecular biology is advancing at a rapid pace; and understanding of human carcinogenesis process in general is moving steadily. Thus, the timing is opportune to support prostate carcinogenesis investigations to take advantage of new technical developments. Exploitation of these recent advances should provide the foundation for major new insights towards identifying the environmental causes and the cellular and molecular mechanisms involved in the transformation of normal and latent prostatic epithelial cells into invasive cancer forms.

The goals of this initiative are to accelerate further understanding relative to carcinogenesis of the prostate gland in animals and man. Integrated studies which would address one or more of the items selected from any one, or from a combination of, the following categories are encouraged. While these should not be considered the only areas of research opportunity, the following aspects of prostate carcinogenesis might be included within the proposed studies:

Cell biology and carcinogenesis. There is a need to establish markers that can identify those prostatic epithelial cells undergoing the various transformation steps. Incumbent in this is the need to identify the cells at risk. Is transformation restricted only to the putative epithelial stem cell, or are all of the epithelial cells in the gland potential target cells?

Carcinogen metabolism. Investigations might include carcinogen metabolism, adduct, and repair comparisons (a) among prostates derived from individual human donors, (b) between prostatic and seminal vesicle tissues removed from the same donor, and (c) between human and animal prostatic tissues. Do stromal cells, hormone balance, or variation in nutrients affect the results? What is the degree of variation among humans in the ability to metabolize carcinogens?

Molecular mechanisms. Very little is known at the molecular level about the specific changes that occur as prostatic epithelial cells undergo the various stages of transformation. Areas that could be studied might include (1) characterizing oncogene activation as a function of transformation stage; (2) delineating the effects of activated oncogenes when transfected into normal and premalignant cells; (3) elucidating the mechanisms whereby putative autocrine growth factor production and/or abnormal expression of growth factor receptors occurs; (4) ascertaining if specific aberrations in intercellular signalling pathways accompany transformation; (5) identifying putative prostate cancer specific suppressor genes; (6) elucidating the molecular changes that result in dysfunction of androgen regulated genes; and (7) determining if specific chromosomal changes are associated with premalignant and/or malignant cells.

Cellular mechanisms. Additional research should be focused on (1) determining if epithelial/mesenchymal interactions play any role in the carcinogenesis process; (2) measuring the degree of cell-cell communication among prostatic cells and ascertaining whether alterations in the pattern of cell-cell communication correlate with either the emergence of the latent tumor phenotype and/or the progression of the latent tumor to clinically apparent malignancy; (3) assaying for growth factors in prostate tissue and seminal fluid; (4) evaluating whether during any specific stages of the carcinogenesis process the cell begins to produce autocrine growth factors or express receptors for growth factors that the normal (or perhaps the latent tumor phenotype) cell does not recognize; (5) establishing specific changes in the growth factor, hormone, nutrient, and ion requirements for growth; (6) determining if the loss of responsiveness by the cells to (putative) growth inhibitors (e.g., hormones, pH, interferons, tumor necrosis factors) occurs during tumor progression; and (7) quantifying changes in cell curface, cytoplasmic and nuclear antigens.

Appropriate models. Presently, there are no established in vitro or animal models that have proven to be adequate for studying all of the aspects of prostate epithelial cell carcinogenesis. Thus, the development of a reproducible, practical method for the experimental induction of prostatic adenocarcinoma is needed. Animal models must incorporate as many of the histopathological aspects of the human disease as possible and ideally, the tumor should metastasize to the bone and other tissues. Optimally, the culture systems should provide for the reproducible transformation of the epithelial cells through the recognizable stages of latent and malignant tumor cells when assessed in an isogeneic or immunologically competent host. In addition, because of possible species differences, it is desirable that culture systems include human prostatic cells. Finally, the model systems should be amenable to use as a screening procedure for assessing whether the rate of transformation can be affected by diet/culture medium composition, hormones, viral/microbial infections, transfected (autocrine) growth factor genes, oncogene activation, and/or the dose and chemical nature of carcinogens and tumor promoters.

In summary, a broad description of important areas of research on prostate carcinogenesis has been proposed for study because limited information is available on these topics. Because of the paucity of adequate studies and investigators working in this area, this initiative is proposed to encourage research on various aspects of prostate carcinogenesis. Consortial, multidisciplinary studies under an RO1 application are

encouraged as well as individual projects that would contribute to understanding of the determinants and mechanisms of prostate carcinogenesis.

This concept was developed by the Prostate Cancer Working Group of the Organ Systems Program. It was the first to be presented to the DCE Board under the revised OSP, in which initiatives for new research are developed in collaboration with division program staff.

David Longfellow, DCE coordinator for the OSP and chief of the Chemical & Physical Carcinogenesis Branch, presented the concept to the Board. Noting that Donald Coffey, chairman of the Prostate Cancer Working Group, was present, Longfellow said, "I feel like someone dancing in front of Baryshnikov, in talking about prostate cancer with Don Coffey here."

Support services for biostatistical and analytical studies. This will be a four year contract, with an estimated total annual cost of $1.2 million.

The Biostatistics Branch of the Epidemiology & Biostatistics Program conducts a broad based program of biometric research, generally categorizable as theoretical research in statistical methods applicable to the design and analysis of experimental, laboratory and clinical and epidemiologic studies of cancer; field research on biometric and epidemiologic methods to improve the conduct of cancer studies in human populations; and collaborative analytical studies that apply biostatistical techniques to provide new leads to cancer etiology and prevention. Although much of the theoretical statistical research can be carried out independently by Branch staff, much of the research on field methods and collaborative etiologic studies requires support to assist in the collection and management of data. Over the past several years, the Branch has obtained this support from resource contracts managed by other branches within EBP. These contractors have been used to assist staff in the collection of information useful for assessing alternative methods in epidemiologic study design, conduct and analysis, and to provide field support for etiologic investigations in which staff are collaborating, including several studies in China.

A direct contract for support of this research is requested in this concept. A separate contract would offer advantages of management and accountability residing in the branch primarily responsible for the work being done. The contract would establish a mechanism for the provision of all of the support services required to conduct a wide variety of methodologic and field studies. Support services provided by the contractor would include development of liaison with organizations and individuals at a local or international level whose cooperation is needed for the conduct of a study; assistance in the design and pilot testing of forms required to conduct field investigations; the hiring, training and day to day supervision of technical personnel; the actual collection of the required data; the data reduction activities involved in field investigations; and the management of data flow to ensure orderly delivery of data to NCI. The contractor will also assist NCI in the provision of on site field supervision and implementation of quality control mechanisms.

Responding to Board member Roy Shore's question on whether there would be a corresponding reduction in the support contracts of other branches which have been utilized in the past, project officer William Blot said that "since there is no additional money available, there will be a reprogramming of funds within the program. DCE Director Richard Adamson noted that the contract total is level except for AIDS.

The remaining concepts approved by the Board will appear in next week's issue of The Cancer Letter.

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, Executive Plaza South, room number shown, National Cancer Institute, NIH, Bethesda, MD 20892. Proposals may be hand delivered to the Exective Plaza Building, 6130 Executive Blvd., Rockville, MD. RFP announcements from other agencies will include the complete mailing address at the end of each.

RFP NCI-CP-95606-21

Title: Environmental cancer studies in prepaid health plans

Deadline: Approximately Dec. 15

The Environmental Epidemiology Branch of the Epidemiology & Biostatistics Program of NCI's Div. of Cancer Etiology is recompeting an ongoing project which is currently being performed by Kaiser Foundation Research Institute of Los Angeles, Oakland and Portland, OR. Multiple awards are planned.

NCI has a need to evaluate hypotheses, rapidly, concerning the environmental causes of cancer. The general aim of this project continues to be the establishment of a collaborative research project which provides EEB with a resource whose priorities could easily be manipulated to rapidly evaluate hypotheses about environmental causes of cancer by analysis of information from prepaid health plans in existence for many years covering large groups of patients with particular cancers and comparable unaffected individuals.

In addition, this resource can be used for exploratory studies to uncover previously unrecognized associations which deserve further study. Another objective has been to explore the unique opportunities for record linkage within these plans and thus utilize data collected for other purposes for assessments of cancer risk.

The main value of this resource is to provide a framework where emergent hypotheses can be evaluated relatively quickly. To some extent, the specific objectives for the next four years will depend upon the nature of these hypotheses as they emerge. However, currently, the specific objectives to be pursued in the first two years of the project will be:

1. Evaluation of the determinants of the risk of second primary cancers in persons developing a first primary malignancy while in the PPHP. Special emphasis will be placed on the risk of leukemia related to total dose of alkylating drugs for treatment of a first malignancy at any site and on the risks of solid tumors in patients treated for a first primary Hodgkin's disease.
2. A case control study of primary cancers of the kidney with emphasis on drug exposure (especially diuretics) and obesity.
3. Attempts to assemble a cohort of persons treated with DES during pregnancy (mothers, daughters, sons) in order to initiate a retrospective and prospective followup study.

The specific topics to be pursued in the later years shall remain open in order to provide the opportunity to either follow up on studies done in the initial years or to pursue new hypotheses of high priority that will evolve in the course of the next several years.

The level of effort anticipated to meet the scope of work would be approximately one third time for a senior scientist (MD or PhD), one third time for a computer specialist, a full time research assistant/ project coordinator and two full time record abstractor /clerks over a four year period.

Contract Specialist: Barbara Shadrick
RCB EPS Rm 620
301/496-8611

NCI-CB-95600-61
Title: Biomedical computing software services in support of the diagnosis program
Deadline: Approximately Dec. 15

This is a total small business set aside with a size standard of $12.5 million.

The Diagnosis Research Program has maintained serum banks for the evaluation and validation of promising serum markers since the early 1970s. Two banks, the Diagnosis Serum Bank and the Breast Cancer Serum Bank, are being more closely integrated. The combined bank will generate data sets requiring the use of existing software and the design and use of custom software for their management and processing. Major tasks include:

A. Processing information related to serum bank requests and maintaining summary information.

B. Generating designs for coded serum panels for transmission to the serum bank contractor for assembly and shipping.

C. Coordinating the development and shipping of panels and tracking the progress of panel assays.

D. Entering and validating assay results and patient clinical data related to completed serum panels.

E. Preparing and mailing clinical data to the investigator upon receipt of completed assay results.

F. Performing statistical analysis on data from serum panel assays and reporting results to the investigator and to the project officer.

G. Maintaining the current inventory and summary information for the Breast Cancer Serum Bank collection.

H. Performing special analyses and maintaining data from studies generated by the Diagnosis Research Program.

This requires the application of existing software or the development of specialized software for data organization, maintenance and analysis. Use of the Div. of Computer Technology's computer system located at the NIH campus is required.

The offeror must demonstrate the ability to meet with the project officer in Rockville, MD, to discuss requirements for special reports involving retrievals of complex data. Then, they must be capable of meeting with experts at the Div. of Contract Research & Technology of at NIH to design appropriate mechanisms for dta retrieval, retrieve the data, prepare an appropriate report as designed by the project officer and deliver hard copies to the project officer in Rockville within 24 hours of the first notification by the project officer.

The incumbent contractor is Information Management Systems. A five year award is anticipated.

Contract Specialist: Charles Jackson
RCB EPS Rm 620
301/496-8611

NCI CONTRACT AWARDS

Title: Analysis of fiber and fiber components in food
Contractor: Univ. of Wisconsin (Madison), $1,072,576

Title: Clearinghouse for ongoing work in cancer epidemiology
Contractor: International Agency for Research on Cancer, $476,500

Title: Case control study of cancer and drinking water contaminants in Iowa
Contractor: Univ. of Iowa, $338,981

FDA Adopts Plan For Drug Approval After Phase 2; Chabner Unconvinced

FDA has decided to go ahead with its plan for speeding approval of new drugs for life threatening or severely debilitating illness, with anticancer agents and new drugs for AIDS patients the presumed primary beneficiaries.

The new procedures were published Oct. 21 in the "Federal Register." They are effective immediately, but FDA will accept comments until Dec. 20.

The plan provides for investigational drugs to be approved for marketing following phase 2 studies, under these conditions:

* After phase 1 studies have been completed to determine toxicities and maximum tolerated doses, the drug sponsor and FDA staff will confer on the design of phase 2 studies. In most cases, at least two phase 2 studies will be required.

* "Once phase 2 testing and analysis is completed and a marketing application is submitted," the rule states, "FDA will evaluate the data utilizing a medical risk/benefit analysis. As part of this evaluation, FDA will consider whether the benefits of the drug outweigh the known and potential risks of the drug and the need to answer remaining questions about risks and benefits, taking into consideration the severeity of the disease and the absence of satisfactory alternative therapy."

* Following marketing approval, phase 3 studies will be carried out.

Bruce Chabner, director of NCI's Div. of Cancer Treatment who has expressed skepticism of the new plan (**The Cancer Letter**, Oct. 21), is not convinced.

"I still don't understand it," Chabner said. "I don't think it will make much difference." In fact, Chabner said, FDA staff does not really think it will result in significant change. He said that Robert Temple, director of FDA's Div. of Oncologic & Radiopharmaceutical Drugs, wrote in a letter recently that the new procedures "don't represent much departure from what we've been doing."

"If FDA will change its approval criteria to include responses and not insist on relative efficacy, that would be an improvement," Chabner said.

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