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## Organ Systems Program Success With Concepts Continues As DCBD, DCE Boards Okay Five More

NCI's Boards of Scientific Counselors are continuing to show great respect for the Organ Systems Program recommendations presented to them. Approval of all five concepts from OSP brought in June to the Div. of Cancer Biology & Diagnosis and Div. of Cancer Etiology Boards raised the total approved under the present system to 18 out of 20. The latest round included three RFAs, with set aside funds, approved by the DCE Board with estimated annual costs

(Continued to page 2)

*In Brief*

## Appropriations Bill Markups Due This Month, With Increases Seen For NCI, NIH And AIDS

**APPROPRIATIONS BILLS** for the Dept. of Health & Human Services, which will include NCI's money for the 1988 fiscal year which starts Oct. 1, will be marked up by the House Labor-HHS Appropriations Subcommittee soon after the July 4 recess, and by the Senate subcommittee probably a couple of weeks later. Both will have healthy increases for NIH and NCI, and whopping increases for AIDS research and education . . . . **ANDREW GAGE**, associate director for clinical affairs at Roswell Park Memorial Institute, has been promoted to deputy director, RPMI Director Thomas Tomasi announced. Gage will be responsible for coordination of clinical research and educational activities. . . . **DAVID BROWN**, vice president for advancement at Virginia Commonwealth Univ., has been named director of development and public affairs at Dana-Farber Cancer Institute by President Baruj Benacerraf . . . **NATIONAL SYMPOSIUM** on "Emerging Technologies and Issues in Cancer Management," scheduled for July 9-10 at Fox Chase Cancer Center, has been canceled because of poor response. . . . **MARY LASKER** and **Ann Landers** were the winners of the 1986 Federation of American Societies for Experimental Biology Public Service Award. . . . **NEW PHS** grant application forms are now available. The form (PHS 398) must be used by NRSA applicants starting with the Sept. 10, 1987 receipt date, and by research grant and research career development award (RCDA) applicants starting with the Oct. 1, 1987 receipt date. PHS has sent copies to each institution business office; additional copies may be obtained from Office Services Section (PHS 398), Div. of Research Grants, NIH, Westwood Bldg Rm 436, Bethesda, MD 20892, phone 301/496-9797.

PDQ Now Offers CME Credit To Physician Users . . . Page 8

RFP Available . . . Page 8

## DCBD, DCE Boards Okay Concepts For Five More Organ Systems Projects

(Continued from page 1)
totaling $2.1 million; and two program announcements approved by the DCBD Board.

Since the present Organ Systems Program became operational four years ago, with working groups for each of the (now) seven sites screening the literature and holding workshops to identify research gaps, only a program announcement on factors involved in breast susceptibility to carcinogens and an RFA on pancreatic cancer case control studies were rejected.

The Organ Systems Coordinating Center, located at Roswell Park Memorial Institute and supported by NCI through a cooperative agreement, manages the program under the direction of James Karr. The seven working groups are for cancers of the bladder, breast, central nervous system, large bowel, pancreas, prostate and upper aerodigestive system.

The coordinating center's budget, which includes costs of convening the working groups, conducting the literature searches, holding workshops and producing newsletters and other publications, is $760,000 a year in direct costs.

The coordinating center cooperative agreement was a five year award, and the National Cancer Advisory Board will have to determine whether the program should be continued sometime within the next six-eight months. If it is, an RFA will be issued to recompete the award.

Discussion of the issue will be on the NCAB agenda for its Sept. 26-28 meeting. Bernard Fisher is chairman of the NCAB's Organ Systems Committee.

The concepts approved by the DCE Board last month would support up to 15 new grants, depending on the quality and type of applications received. The total money set aside for those grants, under the RFA mechanism, is $2.1 million for FY 1988.

The program announcements approved by the DCBD Board have no set aside money and are intended only to encourage investigators to develop proposals for RO1 grants, to go through the regular NIH investigator initiated grant system.

The three RFAs, with the concept statements (edited somewhat to conserve space), appear below, followed by the two program announcement concepts:

Identification of genetic alterations involved in bladder carcinogenesis. An estimated five three year grants would be supported with total first year costs of $650,000; estimated cost for the second year is $700,000, and for the third year, $750,000.

The major goal of this initiative is to increase understanding of the molecular level oncogene alterations underlying multistage chemical carcinogenesis in urinary bladder epithelium. The experimental approach to this goal, as described below, is made possible by recent successes in the development of molecular biological, cellular and in vivo systems for the exporation of urinary bladder carcinogenesis. Collectively, these findings present a unique opportunity to integrate these diverse areas in efforts to achieve the following specific objectives: (1) determine what alterations (mutations, translocations, amplifications) in known cellular proto-oncogenes are important in multistage bladder carcinogenesis in experimental systems; (2) identify other genes which may be involved in the pathogenesis of bladder cancers; (3) use cytogenetic studies to provide clues to the molecular alterations present in bladder cancers; (4) determine the mechanisms by which carcinogens activate proto-oncogenes in bladder cancer tumorigenesis; and (5) determine the role and timing of these genetic changes in the multistage development of bladder neoplasia.

Recent progress in the analysis of genes which are altered in several human and animal tumors might make possible the identification of genetic alterations which underlie the development of human bladder cancer.

There have been four types of genetic alterations so far identified in neoplasms. Single base pair mutations, usually of the ras genes, occur in a large percentage of animal tumors and in some primary human tumors. Gene amplifications are particularly prominent in human neuroblastomas (N-myc) and malignant gliomas (c-erb-1), and occur sporadically in many other tumors. The translocation of the c-abl gene in Burkitt's lymphomas forms the prototype example for this type of genetic change in human tumorigenesis. Finally, deletion of putative tumor suppressor genes occurs frequently in childhood tumors such as retinoblastomas and Wilms' tumors, and also in certain adult neoplasms. The identification of these genetic alterations at the molecular level was often preceded and stimulated by cytogenetic studies which suggested that specific chromosomal abnormalities were present in the affected tumor cells. As a result of all these studies, activation of cellular proto-oncogenes has been strongly implicated in the pathogenesis of several kinds of human cancers. This association of activated oncogenes with the development of human cancers has stimulated research on the biochemical, molecular, and cytogenetic mechanisms by which oncogenes are activated, and on the role such activated oncogenes might have in causing cancer.

Several important findings have resulted from extensions of this research. First, there is now good evidence in several systems that chemical carcinogens cause damage to cells which results in the activation of oncogenes. Thus, oncogenes might be important targets for chemical carcinogens. In experimental chemical carcinogenesis studies, both in vivo and in vitro, the most commonly activated oncogenes found in tumors are members of the ras family (ha-ras, N-ras, and Ki-ras). This is particularly interesting, in that the genes most commonly activated in human cancers, at least as detected by the NIH-3T3 assay, also belong to the ras family.

An additional important concept resulting from recent studies on the role of oncogenes in the development of neoplasia is the demonstration that at least two separate genetic events are required to neoplasti-

cally transform normal cells. This concept is in agreement with epidemiological and clinical studies suggesting that several sequential steps are obligatory for development of a human malignancy.

The possibility that one or more of the genetic events leading to cancer may be recessive in nature has been a recurring theme in cancer research, and is supported by some experimental evidence. For example, fusion of cancer cells with normal cells often suppresses the neoplastic phenotype. In addition, cells from several different tumor types, including human bladder cancers, show nonrandom loss of heterozygosity of specific chromosome sequences suggesting that recessive genetic changes contribute to the development of cancer.

State of the art for studies of the molecular and cellular biology of bladder cancer. The human urinary tract is lined by transitional epithelial cells. The epithelium of the normal bladder is stratified and the epithelial cells follow a program of growth and terminal differentiation, and eventually slough off and are found in the urine. This pattern of normal growth and differentiation is disrupted when cancer develops. It has been hypothesized that when cancer develops, genes that control normal growth and differentiation are altered. Although the genetic alterations that are crucial to malignant transformation may be very specific if not unique, the actual genetic damage produced by chemicals and radiation is much more random. From a descriptive viewpoint, this broad spectrum of damage may be responsible for heterogeneity in the biologic behavior of tumors. Furthermore, the nature of the genetic lesions might account for genetic complexities that preclude the identification of a single characteristic that is associated with all malignancies. From a functional perspective, it is not surprising that different oncogenes, as well as the same oncogenes, may be active in cancers derived from the same cell type, as well as in cancers from different cell types. Conceivably, exploration of these expressions of genetic damage could contribute, not only to our understanding of the carcinogenic process, but also to practical insights regarding tumor identification and prognosis for those genes involved in later stages of malignant progression.

A search for activated cellular oncogenes in human bladder cancers has led to only partial success. Although the first activated ras gene was discovered in a human bladder cancer cell line, a subsequent search for such activated ras genes in fresh clinical biopsies of human bladder cancers showed activated ras genes present in less than 10% of cases. Thus, the examination of bladder cancers with a view to identifying other activated genes is very relevant and important. Furthermore, the current association of ras with a small but significant percentage of human bladder cancers also deserves further investigation. Ras activation has neither been rigorously demonstrated to be causally associated with the development of bladder cancer, nor has the stage in the development of bladder cancer at which ras might be activated been identified. Since bladder cancers are typically multistage, this information has obvious relevance to understanding the etiology of the disease, and to the development of molelcular markers for the diagnosis and prognosis of bladder cancers. Such questions can be approached through appropriate experimental systems.

Mammalian bladder urothelium is a particularly useful organ system for studies of multistep chemical carcinogenesis. Epidemiological evidence associates exposure to environmental chemicals with an increased risk of bladder cancer, particularly those compounds that are classified as aromatic amines. The development of bladder cancers is characteristically multistage in nature. Excellent rodent model systems have been developed to study the pathogenesis of bladder cancers by chemical carcinogens. Such model systems have some special advantagaes for studies of activation of cellular proto-oncogenes by carcinogens. For example, tumors of different grades and stages and of different histopathologies are obtained in many of these systems. An analysis of such tumors would be useful for correlating molecular changes with tumor pathology. Tumors in animal model systems have been induced using several important classes of chemical carcinogens including nitrosoureas, nitrofurans, polycyclic hydrocarbons and arylamines.

In parallel with the demonstration of tumor induction by these compounds, biochemical studies have identified many of the pathways by which these compounds undergo metabolism to yield products that can react with tissue macromolecules such as nucleic acid and protein. This process, often referred to as "metabolic activation," has been associated with tumor induction in a number of systems. The structures of nucleic acid adducts formed as a consequence of these metabolic activation events have been elucidated, and progress is evident in better understanding how the adducts can alter the function of DNA. Thus, it has been possible to introduce adducts into plasmid DNA at a single, specific site of infectious viral DNA, introduce that DNA molecule into a bacterial cell, identify the mutated phage progeny of the adducted DNA and determine the alteration in nucleic acid sequence responsible for the mutagenic event. Similar approaches with randomly modified DNA molecules has been carried out in mammalian cells, including demonstration of the activating mutagenic effects on proto-oncogenes encoded in these plasmids. Application of such technology should provide the opportunity to positively associate the genetic effecs of chemical carcinogens to the transformation process.

In addition to the animal model systems, several in vitro cell culture systems have been effectively utilized to study the steps of transformation in mammalian bladder urothelium. Recent advances in cell culture techniques have resulted in reports of transformation in vitro of both human and rodent urothelium. Studies with cultured human urothelium could complement studies using animal models, and would provide direct information on the transformation of human bladder epithelium.

**Model systems.** Several model systems for the study of chemical carcinogenesis in the mammalian urinary bladder already exist. It is anticipated that these efforts would incorporate these systems, e.g. for multistage transformation, and others developed with other with other biological systems that can facilitate the experimental approach to the role of genetic alterations in the genesis and development of bladder tumors. Either animal model systems or cell culture systems (human or rodent) could be used as long as these have well defined biological endpoints.

**Chemical carcinogens.** Although emphasis should be placed on the study of the role of human bladder carcinogens wherever possible, highest priority should be placed on those approaches which are likely to provide the most detailed molecular information in biological systems pertinent to bladder tumor induction. Thus, attempts might be made to elicit biological responses with metabolites of carcinogens which are expected to be subject to metabolic activation in urinary bladder cells, as for example N-hydroxyarylamine derivatives. This would avoid the possibility that the target bladder cells could respond because of inadequate levels of N-oxidation potential. It is envision, moreover, that it should be possible to employ DNA vectors which carry the potential for eliciting cellular transformation, e.g. proto-oncogenes, when modified by carcinogens. This approach

should permit the direct exporation of biological responses to carcinogens introduced into the DNA at single, specific sites, following transfection into mammalian cells.

Biological endpoints of transformation. In vitro systems should utilize well defined endpoints to assay for transformation, such as quantifiable changes in growth requirements, development of anchorage independent growth, and the ability to produce tumors in appropriate animals. Tumors should be characterized with specific reference to ability to invade and metastasize. In vitro systems should utilize as the final endpoint the induction of invasive bladder tumors in animals. The final stage should optimally be preceded by intermediate steps, such as dysplasia, metaplasia and noninvasive neoplasia.

Cytogenetic and molecular genetic endpoints of transformation. An objective of the RFA is to stimulate research on the molecular and cytogenetic events in bladder cancers, susceptibility of systems to cytogenetic analysis (translocations, intrachromosomal deletions, and changes in chromosome numbers). Transformed cells should be analyzed for alterations to cellular genes thought to be important in the neoplastic process by analysis of isolated DNA and by use of in situ hybridization techniques. The technology employed should be able to detect base substitutions, frameshifts, translocations, amplifications and loss of genes (or their reduction to homozygosity). The altered expression of specific genes, in the apparent absence of a genetic alteration affecting the gene, might be an avenue of investigation into the role of control sequences as compared to structural genes.

The proposed studies should represent a multi-disciplinary effort, possibly involving collaboration among pathologists, molecular biologists, tumor biologists, cytogeneticists and experts in chemical carcinogenesis.

**The concept** was presented by Bert Vogelstein, Johns Hopkins, a member of the Bladder Cancer Working Group.

"I have reservations about trying to generate something like this," Board member George Vande Woude said. "If a person has a model system,it is up to him to develop it and generate the expertise, put together a group. The person who has the system is the key."

"When this goes to a regular study section," Vogelstein responded, "they say it is a program project in RO1 clothing. It falls between. It would be killed in a molecular biology study section."

"My point is the area is more than adequately stimulated," Vande Woude said. "The problem I have is, who says we should focus on bladder cancer versus lung cancer? Anyone working in this area should come in for support."

"The Organ Systems Program focuses on sites important to humans," Board member Lee Wattenberg said. "Frequently, the experimentalist focuses on what is convenient. I think it is important to emphasize bladder cancer."

"People tend to use existing models," Board member Peter Magee said. "This is a whole new area that will not be studied without this (RFA)."

The motion by Board member William Benedict to approve the concept was adopted on a 10-2 vote, with Vande Woude and Anna Barker opposed.

In vitro transformation of human and animal mammary epithelial cells by chemical carcinogens. An estimated five grants, each for five years, would be awarded at a total cost of $700,000 for the first year.

This project aims to search for methods by which efficient transformation of human and animal mammary epithelial cells to malignant cells can be obtained in vitro by chemical carcinogens. Specific objectives are (1) to develop in vitro conditions that optimally select for growth of mammary tumor cells and favor this over growth of normal mammary cells; (2) to define conditions that increase the frequency of transformation of mammary epithelial cells in vitro; (3) to delineate markers that indicate specific stages of in vitro transformation and distinguish particular preneoplastic states in the multistep process; and (4) to identify markers or assays of mammary epithelial cell transformation that correlate with the tumorigenicity of transformed cells in vivo (as, for example, in athymic, nude mice) and to develop improved in vivo systems for assaying tumorigenicity.

Carcinogenesis requires, at minimum, that the initial step allow a cell to compete effectively, in terms of proliferation, with its neighbors, and that the resulting clonal population have a long, possibly indefinite capacity for self renewal. In transformation, high frequency and yield are also important for feasible study of the process, and markers to identify and follow the various stages in the process would be extremely valuable. To define at the molecular level the specific alterations responsible for each stage of transformation to malignancy is of major important for understanding cancer and carcinogenesis. However, this project seeks practical answers to difficulties in mammary epithelial transformation rather than mechanistic explanations of the underlying causes or events. The goal is to achieve efficient, in vitro chemical transformation of both roden and human mammary epithelial cells that parallels insofar as possible mammary tumorigenesis in vivo, and the concern is to delineate conditions that can reproducibly accomplish this aim. This challenging problem is clearly complex and has not proven amenable to easy solution. It is, however, critical for an understanding of the carcinogenic process and of any way to alter this process. To approach the problem, primary emphasis is being placed on the following:

1. Improved in vitro culture systems and conditions, and especially delineation of the conditions that favor and select for the growth of transformed cells rather than normal cells. Systems would preferably use defined medium, and the research would identify essential or facilitating factors that need to be added to achieve optimum tumor cell growth, i.e., specific growth factors, hormones and other important supplements. Optimal combinations and levels of these would also be defined.

2. Increased efficiency of transformation in an in vitro process that parallels as close as possible mammary tumorigenesis in vivo. This would include determination of protocols and conditions that result in high frequency of the transformation event, e.g., choice, treatment regimen and level of carcinogen, as well as conditions for optimum growth of the transformed cells. It might include delineation of the most vulnerable growth phase or state of the target cells, as well as their most appropriate environment. It could include identification of mammary epithelial cell types or stages most susceptible to transformation, e.g. perhaps embryonic cells or cells from young, virgin hosts, in which mammary gland is not yet fully mature and largely undifferentiated. Identification of such cells and conditions for animal systems might be followed by exploration of the relevance of the findings for readily transformable mammary epithelial material from human hosts.

3. Phenotyopic markers of preneoplasia, readily identifiable in vitro and preferably able to be quantitatively assayed, that can help define and follow the sequential steps in tumorigenesis; also, comparison of these with equivalent markers for frank neoplasia. This could include, e.g., specific cell surface antigens or such molecular correlates as altered oncogene expression. New markers should be

explored; examination could also be made of correlations with already reported markers of transformation, such as immortalization and anchorage independent growth. Recent exciting studies on the role of oncogenes and oncogene products in cell transformation indicate that definition of underlying mechanisms at the molecular level is both feasible and promising. The relevance of such underlying molelcular events to other, descriptive, identifiable properties of transformed cells needs equivalent attention. Thus, it could be important to examine altered expression of cellular oncogenes in systems in which high frequency of transformation has been achieved. A search for such molecular correlates could follow naturally from development of optimal systems, as defined in No. 1 and 2 above.

4. Assays for markers of mammary epithelial cell transformation (i.e., in vitro phenotypic expressions of transformation) that best correlate with tumorigenicity of the transformed cells in vivo, and improved in vivo assays for tumorigenicity. Currently used in vivo host systems (e.g., the athymic, nude mouse; the gland free, mammary fat pad of syngeneic hosts) do not appear to accept readily transplantation of primary mammary carcinomas, rodent or human, unsyngeneic hosts) do not appear to accept readily transplantation of primary mammary carcinomas, roden or human, unlike results with many breast carcininoma cell lines. Similarly, mouse mammary epithelial cells transformed in vitro have also provided only low yields of carcinomatous outgrowths in vivo. An important objective would be to improve the receptivity of in vivo host systems to transformed mammary epithelium. This could be accomplished by modification of the host immunological and/or endocrinological systems. Other immunotolerant in vivo models (e.g., the NK cell deficient beige mouse, chick embryo skin, etc.) might be examined and assessed for their potential as recipients of transformed mammary epithelial cells. It is important to define more specifically what conditions and factors transformed cells require for final expression of neoplasia in vivo. The development of improved in vivo assays for tumorigenicity, and of markers of transformation that best correlate with tumorigenicity in vivo, could be explored first in the more approachable or more promising animal cell systems, and the findings then could be extrapolated to other, more difficult systems. Certainly, assays of potential relevance for transformation of human mammary epithelium are an ultimate objective.

Carefully designed studies are sought from investigators who have expertise in cellular and molecular biology and experience in techniques of cell culture in vitro. The primary challenge will be working out optimal animal or human epithelial cell systems for chemical carcinogenesis in vitro. Currently available systems may well have to be modified or further developed for probing these questions adequately; new systems could also be explored. Recent advances offer promise that achievement of the proposed aim can be attained. To answer the questions being asked, the studies sought will require detailed exploration of specific experimental conditions for optimal transformation, and painstaking correlation of various phenotypic alterations with stepwise development of preneoplasia and neoplasia; these alterations can be ones already described or others newly defined. A respondent could address any of the four aspects considered above, singly or in concert. Collaborations are not required, but appropriate multidisciplinary interaction is welcomed. A good example would be collaboration between cell biologists and molecular biologists to explore altered oncogene expression or levels of gene products as molecular correlates of other phenotypic alterations in the transformation process or in the stepwise progression to malignancy.

**Daniel Medina**, Baylor College of Medicine, presented the concept on behalf of the Breast Cancer Working Group.

Benedict expressed his "strong" opposition to the concept. "There are a lot of people who could write this as an RO1," he said. "This should not go out (as an RFA)."

Medina responded that the working group had done a computer search and had found only four groups doing studies along those lines.

Board member Thomas London, commented, "This is a narrowly focused research objective. It seems to me that a program announcement would be sufficient."

"That would go to a regular study section," Medina responded. He was supported by Board member Janet Butel who said, "I don't think a grant could ever get funded to do this," going through the NIH study sections.

Barker suggested that since "you are really trying to increase participation in this approach," a program announcement could be tried first. "The chemical pathology study section would not look kindly on this," Medina insisted.

Despite the objections, the concept was approved by a 6-4 vote with two abstentions. Benedict, Barker, London and Lawrence Fischer voted against it.

Mechanisms of alcohol and tobacco related carcinogenesis of the oral cavity. Five awards, each for three years, would be supported with an estimated first year total cost of $750,000. Second and third year costs were estimated at $795,000 and $842,700.

Epidemiologic studies have demonstrated that there are at least two tobacco related causes of oral cavity cancer: the combination of chronic alcohol consumption and cigarette smoking, and snuff dipping. The specific objectives of this concept are to use appropriate experimental animal models, organ culture systems, or cell culture systems to elucidate the mechanisms by which tobacco use increases the risk for squamous cell cancer of the oral cavity. Studies related to oral cancer induction by the combination of chronic alcohol consumption and tobacco smoking, or snuff dipping, are appropriate.

Appropriate studies could include the development of animal models, or cell/organ culture systems for investigating the mechanisms of oral cavity cancer induction by tobacco and alcohol. Thus the development of a reproducible animal model of oral cancer, in which the carcinogen was tobacco smoke or its condenstate, or a compound or compounds present in tobacco smoke, and in which tumor incidence was enhanced by alcohol, would be most useful. Ideally, the model should have essential characteristics in common with the human setting. In addition, an animal model for induction of oral cavity cancer by snuff is needed for further investigations of snuff induced carcinogenesis of the oral cavity. Animal models which show precursor mucosal changes associated with cancer development and similar to those observed in humans would also be useful. Cell culture and/or organ culture systems which undergo changes indicative of neoplastic development in response to tobacco or tobacco smoke and its constituents are needed. Such models might focus on tumor initiation, tumor promotion, or cocarcinogenesis.

Appropriate studies might also include the effects of alcohol on the metabolic activation, DNA binding, and DNA repair of carcinogens present in tobacco smoke; these studies should be carried out in tissues or cells of the oral mucosa. The effects of alcohol on oncogene activation or related changes induced in oral tissues by tobacco smoke constituents would also be of interest. Further studies are needed on the relationship of the nutritional deficiencies and oxidant imbalances associated with alcohol consumption and the

susceptibility of oral tissues to carcinogenesis by tobacco smoke and its constituents. Investigations of the effects of alcohol on the penetration and absorption of tobacco smoke and its constituents through the oral mucosa and on the pharmacokinetics of tobacco smoke constituents, as it relates to oral cavity cancer, would also be useful.

In addition to the development of animal models or culture systems, further research on the mechanisms of oral cancer induction by snuff is necessary. Appropriate studies might focus on synergistic effects in snuff carcinogenesis leading to the identification of factors such as virus infection or tobacco constituents, which either enhance or inhibit oral cancer induction by snuff. Investigations of the mechanisms of these synergistic effects are needed.

The studies proposed in this concept are essential to understanding the mechanisms of tobacco and alcohol induced oral cavity cancer. These mechanisms are likely to be distinct from those tobacco induced cancers of other sites. Although mechanistic studies in carcinogenesis arer frequently the subject of conventional grant applications, research focused on the mechanisms by which tobacco and alcohol induce cancer of the oral cavity is limited at the present time.

**Stephen Hecht**, of the American Health Foundation, presented the concept for the Upper Aerodigestive System Cancer Working Group. The concept was approved unanimously without dissent after Board member Dietrich Hoffmann commented, "In the (regular NIH) study sections, the attitude is, smoking causes cancer so why the hell study it?)."

Evaluation and utilization of transgenic animal models in studies of pancreatic cancer. This and the following concept were approved unanimously by the DCBD Board as program announcements. There are no set aside funds, and the grant applications would be reviewed by regular NIH study sections.

The goal of this announcement is to stimulate research in one or more of the following areas: Utilize the currently available transgenic mouse model of acinar cell pancreatic cancer in studies of mechanisms, modulation and chemoprevention of carcinogenesis, cell of origin, and tumor markers; establish and use a transgenic mouse system in studies of ductal cell pancreatic cancer; and establish and use transgeneic systems for pancreatic cancer in animal species which have a greater propensity for ductal cell adenocarcinoma, such as the Syrian hamster.

Few investigators are involved in research in pancreatic cancer and few have been attracted to the animal models currently available for the study of this disease. Production of transgenic mice containing various oncogenes or transforming genes provides a new tool for analyzing how these genes function in development and tumorigenesis. The recent development of transgenic mouse models of pancreatic cancer would provide experimental systems which are more accessible, reliable and manipulable and would provide a stimulus for more scientists to study cancer of the pancreas.

Approaches to the establishment and study of pancreatic ductal cell adenocarcinoma models.

Currently available acinar cell adenocarcinoma transgenic models. Introduction into the germ line of the pancreatic elastase-SV40 gene constructs have provided strains of mice in which 100% of the progeny develop acinar cell pancreatic cancer. Four such strains have now been produced, and some are now homozygous in regard to the genetic construct. These systems need to be evaluated with regard to histopathologic and developmental features, and should be used in studies on mechanisms and control of carcinogenesis. They may also be appropriate for studies on tumor markers for pancreatic cancer.

Transgenic mice containing ductal cell specific genes. It should be possible to attach an oncogene to the promoter enhancer region of a gene specific for pancreatic ductal cells, thereby targeting the transformation events to ductal cells. Laboratories which have identified genes or gene products specific for pancreatic ductal cells and which can demonstrate expertise in transgenic systems may be eligible for development of a pancreatic ductal cell transgenic model.

Establishment of pancreatic tumor models in other animals. The observations that chemical carcinogens induce primarily ductal cell tumors of the pancreas in the Syrian hamster but primarily acinar cell tumors in the rat raise the possibility that the histopathologic appearance of the tumor is controlled by species specific determinants. If the difference in phenotypic appearance of transgenic adenocarcinomas is similarly a result of how the host species handles and reacts to the introduced construct, then this model may provide answers to the questions of cell lineage and control of differentiation in these tumors. The immediate obstacles to developlment of such models are biological, such as the availability and manipulability of sufficient numbers of hamster eggs.

Researchers with expertise in the areas of cellular and molecular biology, carcinogenesis, or development of transgenic animal systems would be appropriate applicants for this announcement. However, multidisciplinary collaborative teams including reproductive biologists and molecular biologists involved in transgenic systems, as well as experts in carcinogenesis of the pancreas, may enhance the prospects for success.

**James Jamieson**, Yale, and **Daniel Longnecker**, Dartmouth, presented the concept for the Pancreatic Cancer Working Group.

"Does it make sense for each working group to come to us each year asking for development of transgenic models, or should a broader program announcement include them all?" Board member Robert Perlman asked.

Jamieson responded that there could be overlapping areas and that the announcement could be combined with other organ systems. "I'm a firm believer in cross fertilization," he said.

Andrew Chiarodo, chief of NCI's Organ Systems Section, also responded. "Why limit this to pancreas cancer and not make it a general announcement? That question comes up all the time. There is some cross fertilization, but as each group looks at an area, it sees not much going on." Chiarodo said that with the program announcement, the group hoped "to encourage people working in other areas to include pancreas, and perhaps target some of their efforts."

Role of growth regulatory factors in normal neoplastic prostate.

Objectives of this program announcement are to identify and characterize growth regulatory factors produced by normal or neoplastic prostate cells, to determine their possible autocrine or paracrine functions in normal growth and neoplasia, and to define the role of growth factors in the pathogenesis and metastatic spread of prostate cancer.

The prostate displays a wide range of diversity for growth and metastatic potential. Prostate cancer is associated with an unusual and extremely high prevalence of latent or dormant cancer that is clearly identified on pathological examination, but which in most cases will never grow further to become clinically manifest. About 10% of all men 50-59 years of age and about 50% at 7-79 have this latent form of prostate cancer. Only a very small fraction of these latent cancers will ever grow to become clinical prostate

cancer. For unknown reasons growth is held in check in 90% of these latent prostate cancers and this is by totally unknown biological mechanisms. However, those latent cancers that are subsequently activated to grow produce a mortality rate that makes prostate cancer the second leading cause of cancer deaths in U.S. males.

Since the human prostate exhibits a high incidence of apparently dormant cancer cells and a marked diversity of apparent growth rates and spread, a special effort to foster research on the nature or roles of growth regulatory factors in normal and neoplastic prostate could exploit these features in a way that would advance the understanding of the mechanisms underlying the pathogenesis of prostate cancer.

A characteristic property of the prostate is that it contains a high concentration of androgen receptors. Androgen receptors exhibit a high affinity and specificity for androgenic steroids and these steroid receptor complexes bind to DNA in androgen responsive genes. Recently the genes coding for two intranuclear steroid receptors, i.e., glucocorticoid and estrogen, have been cloned and sequenced. Both have segments of nucleotide sequences very similar to a segment of the oncogene, vErb A, which does for a nuclear protein. Other oncogenic products have been demonstrated to have sequence homologies similar to proteins that are important mediators of hormone action on target cells. It is therefore likely that growth factors within the prostate may be related to oncogene products. There is also the possibility that androgen dependent cells within the prostate are transformed to an androgen independent state by alterations in growth factor regulation. Thus, studies on growth factors in the prostate may elucidate alternative mechanisms by which androgens regulate prostate function and may contribute to understanding how cancer cells become androgen independent. The feasiblity of such a mechanism is noted in a recent report on the MCF-7 human breast cancer cell line which described the activation of growth factor secretion in tumorigenic states of breast cancer induced by 17 beta estradiol of v-Ha-ras oncogene, and suggested that a coordinate increase in growth factor secretion by human breast cancer may contribute to its escape from estrogen dependence.

Project description: Observations suggest that autocrine, paracrine and endocrine factors are involved with the regulation of prostate growth. It is timely to encourage research efforts to understand how normal prostate growth is controlled and regulated and how these controls are altered or uncoupled in both androgen sensitive and androgen insensitive autonomous prostate cancer growth and metastasis. This initiative is intended to stimulate research on prostate growth regulatory factors and address factors involved with stimulating DNA replication, and altering rates of cell death. The following describes examples of plossible approaches. It is not implied that any single applicant should pursue all or any of these examples. Other novel approaches with appropriate rationales are encouraged.

A. Isolate, identify and characterize prostate growth regulatory factors including preparation of complementary DNA probes.

This approach would include the possible isolation and identification of prostate growth regulating factors (stimulators and/or inhibitors) from normal and neoplastic prostate. Development of new animal and human prostate stromal and/or epithelial assay systems is encouraged since growth factor effects on different cell types may vary and such assay systems are essential for the identification of prostate specific factors. Growth regulatory factors need to be characterized in comparison to the biological activities of other known growth factors and purified for partial sequencing and production of polyclonal or monoclonal antibodies. Further structural analysis by isolation of cDNA probes from animal and human prostate cDNA libraries is encouraged. Obtaining the full nucleotide sequence of prostate growth regulatory factors will make it possible to derive the amino acid sequence for comparison with sequences of known growth factors and oncogenes.

B. Identify target cells for prostate growth regulatory factors, i.e., prostate stromal cells, prostate epithelial cells, bone cells and androgen sensitive vs. androgen resistant prostate cancer cells.

Biological activity of growth factors in the prostate could be pursued by identifying specific cell surface receptors and by measuring the growth responses of different prostate cell types. Studies would establish the tissue and species specificity of PGRFs responsive cell types. This could include a search for target cells within bone. Using isolated cultures and cocultures of stromal and epithelial cells, it could be determined whether one or both cell types is responsive to PGRF and whether PGRF production by one cell type has paracrine effects on adjacent cells. Growth regulatory factor interactions and effects (proliferation and death) on normal prostate cells might be compared with androgen sensitive and insensitive cancer cells. It would be important in this connection to determine the effects of a variety of hormones and growth factors on target cell responsiveness to PGRFs. For example, it will be important to understand the factors that influence growth regulatory factor receptors on target cells.

C. Localize the site of production of prostate derived growth factors.

The site of production of PGRFs could be determined by immunocytochemical methods using specific antibody probes and by in situ hybridization with cDNA or synthetic oligonucleotide probes. Such studies should indicate where PGRFs are produced within the prostate, that is, in stromal, epithelial or other cell types.

D. Determine the patterns of hormonal regulation of PLGRFs and investigate the role of growth factors as hormones.

It has long been recognized tht prostate development and growth are regulated by the male hormone, dihydrotestosterone. It is becoming increasingly suspect, however, that this effect of androgen is not a direct action on DNA synthesis, but rather one mediated by other intracellular regulators. From what is known about cell cycle control, it is likely that growth regulatory factors mediate androgen control of prostate growth. Thus, it will be important not only to determine whether growth factors are responsive to androgen stimulation of normal and neoplastic prostate, but to learn also whether other hormones and growth factors stimulate PLGRFs.

E. Determine the role of oncogenes in mediating hormone and growth regulating factor effects on normal and neoplastic prostate cells.

Because of the close relationship between growth factors and oncogenes it would be of interest to identify effects of growth regulating factors on cellular oncogene expression.

**Donald Coffey**, Johns Hopkins, and **Donald Tindall**, Baylor College of Medicine, presented the concepts for the Prostatic Cancer Working Group.

"I have the feeling that the Organ Systems Program is responding to what is happening," Perlman said.

"That is absolutely correct," Coffey said. "Remember, our charge is to analyze the field, find an area whose time has come, and attract people to come in and exploit it. This program announcement is saying, 'We need help in this field.'"

Coffey noted that NCI has $55 million in breast cancer research, only $9 million in prostate cancer grants.

## 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-CO-74112

Title: Screening, indexing, abstracting and keying of cancer related literature for the International Cancer Research Data Bank

Deadline: Aug. 24

This project will provide input to the Cancerlit data base. This input involves the acquisition, screening, abstracting, indexing and keying of records representing cancer related documents consisting primarily of nonserial publications including abstracts of papers presented at meetings, books, government reports, theses, and monographs. A limited number of serials will also be processed. The output of these operations will be magnetic tapes containing complete bibliographic citations, abstracts and index terms representing the selected articles and documents.

For this project, offerors must provide indexing and revisor personnel who are certified by the National Library of Medicine. Offerors must have a telecopier system which is compatible with a Xerox Telecopier, Model 485. Offerors must also have a configuration of CRT terminals/computers with sophisticated software packages capable of generating and decoding tapes in digital VAX proprietary file compression format.

This project is a recompetition of the work being done by Information Ventures Inc., of Philadelphia. It is a 100 percent small business set aside.

Contract Specialist: Elaine Larison
RCB Blair Bldg Rm 314
301/427-8877

## Physicians Can Earn CME Credit For Using PDQ Through NLM

Category 1 continuing medical education credit is now available to physicians who make online use of PDQ, NCI's cancer treatment information data base, through the National Library of Medicine.

Accredited by the Accreditation Council for Continuing Medical Education to sponsor CME for physicians, NIH has certified that this activity meets the criteria for one credit hour for each hour of actual time online with PDQ in Category 1 of the Physician's Recognition Award of the American Medical Assn. Credit is available to physicans or physician's assistants only.

"In addition to its CME benefits, PDQ increases our potential to save lives by reducing the delay between the communication and application of cancer treatment advances," NCI Director Vincent DeVita said in making the announcement about the benefits.

PDQ, and subsequent CME credit, is available by individual subscription through NLM's MEDLARS computer system, which is accessible at nearly 8,000 medical libraries and health care organizations in the U.S. PDQ can be used over standard phone lines on any computer terminal that can accommodate 80 characters per line of test.

PDQ users may receive CME credit by submitting copies of their PDQ CME evaluations--available in the PDQ news file--every six months. Cumulative records of online time are easily stored within the system. Billing records also can document access time.

PDQ was developed in 1984 in cooperation with NLM to give physicians rapid access to state of the art cancer information as well as a full range of cancer treatment options and information to support clinical decision making. It enables clinicians to keep abreast of advances in treatment, to identify appropriate clinical research trials for cancer patients, and to identify specialists for consultation or referral.

PDQ yields complete and concise information on the prognosis, cellular classification, staging classification systems, and therapeutic alternatives--both standard and investigational--for all major tumors as well as some rare but highly responsive malignancies. Physicians also can find references to critical seminal or update papers reporting significant clinical research data.

PDQ is the first data base to encompass an entire medical specialty using state of the art computer technology. The information in PDQ is reviewed and updated monthly by experts drawn from academia, research and clinical practice in all medical specialties brought to bear in the treatment of cancer.

Written inquiries should be sent to PDQ, International Cancer Information Center, NCI, Bldg 82 Rm 103, Bethesda, MD 20892.

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