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ACS Community Demonstration Projects Complete, Reach Target Populations, Teach Many Lessons

The American Cancer Society's three demonstration projects on community cancer detection, education, and prevention for socioeconomically disadvantaged populations, initiated in 1989, have been completed, and the Society held a workshop recently to evaluate them.

Among the conclusions reported to the ACS board this month by

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In Brief

Fred Hutchinson Center Celebrates Massive Move Of 36 Labs, 400 Employees To New Campus

FRED HUTCHINSON Cancer Research Center, Seattle, recently celebrated completion of the move of 36 research laboratories and support services to three new buildings at South Lake Union, two miles north of the center. The center held a ribbon-cutting ceremony earlier this month. More than 400 employees and their equipment were moved, including the Div. of Basic Sciences, the Program in Molecular Medicine, some shared resources, and laboratory programs of the Public Health Sciences and Clinical Research divisions. The center plans over the next eight to 10 years to construct an entirely new campus at the site to bring together all employees. . . . **RONALD LEVY** has completed his term as chairman of the NCI Div. of Cancer Treatment Board of Scientific Counselors. Others completing terms on the board include **Robert Baehner, Paul Carbone, Ralph Weichselbaum** and **Joanne Stubbe.** They will be replaced by **Sidney Hecht**, Univ. of Virginia; **Ellen Vitetta**, Univ. of Texas, Southwestern Medical Center; **Zvi Fuks**, Memorial Sloan-Kettering Cancer Center; **Charles Coltman**, Univ. of Texas San Antonio; and **Beverly Mitchell**, Univ. of North Carolina. . . . **THREE MEMBERS** of the NCI Div. of Cancer Etiology Board of Scientific Counselors have completed terms of five years or longer: **James Felton, Larry Fischer** and **Marcel Baluda**. . . . **NATIONAL ACADEMY** of Sciences recently inducted 60 new members, including: **Francis Collins**, new director of the NIH Human Genome Project; **Peter Howley**, chief, NCI Laboratory of Tumor Virus Biology; **George Vande Woude**, director, ABL-basic research program, Frederick Cancer Research & Development Center; and **James Rothman**, Memorial Sloan-Kettering Cancer Center. Howley announced his retirement from NCI as of July 1 to become chairman of the Dept. of Pathology, Harvard Medical School. . . . **KATHLEEN FOLEY**, chief of the Pain Service, Memorial Sloan-Kettering Cancer Center, has been elected to the Institute of Medicine.

ACS Community Demonstration Projects Reach Target Populations

(Continued from page 1)

Robert Schweitzer, who was ACS president when the projects were implemented, were:

▶ After three years, the Harlem, Miami, and West Oakland (CA) projects have demonstrated the feasibility of reaching underserved populations, especially socioeconomically disadvantaged and minority women, with cancer prevention and low or no cost cancer screening and followup services.

▶ The projects overturned the myth that poor urban populations will not utilize these types of cancer control services. They demonstrated that if the services are accessible, available, and delivered in a culturally sensitive, humane, and caring manner, the people will come.

▶ Early detection services must include patient followup services. It would be irresponsible and do the underserved a great disservice to detect cancer and then allow it to go untreated. While none of the projects provide diagnosis or treatment, each project ensured that followup diagnostic and treatment services were available for anyone with a questionable or positive screening.

The three demonstration projects were ACS' response to the findings from seven regional hearings on cancer and the poor (**The Cancer Letter**, July 21, 1989).

The Society's national office provided $1.5 million for the three year projects which were carried out by the local ACS divisions and units. Three additional projects were later initiated, in Atlanta, West Virginia, and Marshfield, WI. A total of $10 million has been raised from local and private sources to support those three.

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Goal To Expand Across U.S.

"It is time to turn the initiative over to the divisions and units for further implementation and development," Schweitzer said. "Our future plans include diffusing the lessons learned throughout the organization. We also plan to develop a 'how to' book of guidelines out of the lessons that were learned."

The Society's goal is to establish similar projects in every area of the U.S. with significant numbers of disadvantaged and underserved people.

Purpose of the projects was to demonstrate how to implement cancer prevention and control programs that ensure high quality, accessible, and affordable screening and early detection services for targeted populations, especially the socioeconomically disadvantaged and underserved.

Each of the projects targeted poor and underserved populations, provided educational services, provided detection and screening services, and ensured and monitored followup care.

"The function of a national demonstration project is to learn from mistakes so that divisions will not have to make those same mistakes," Schweitzer said. "And we learned a great deal from our mistakes as well as our successes."

Involve The Community

The first lesson learned "is probably the most important," Schweitzer said. "Involve the community in the project from the beginning to the end, throughout the life of the project. We learned this lesson the hard way, by failing to adequately included divisions, units, and other interested community groups and individuals in the beginning stages of the projects.

"This was to a great extent unavoidable in that there was a need to act quickly after the hearings and utilize existing facilities to avoid long start up periods," he said. "However, not including the local ACS and other important community groups created a built-in animosity that was difficult to overcome and acted as an obstacle in the early going."

The later projects in Atlanta, West Virginia, and Wisconsin avoided those pitfalls by including local ACS and community personnel in the planning phases.

"Once the original projects were up and running, however, they successfully involved ACS divisions and units and other community institutions and organizations," Schweitzer said.

"Each project is located and embedded in a network of existing institutions. None are outsiders coming into the community."

The projects include local or nearby medical

schools, hospitals, county and city health departments, neighborhood clinics and health centers, major cancer centers, and churches.

Early Mistakes, Lessons Learned

Lesson number two, Schweitzer said, "is the need to conduct a community assessment to determine the community needs and resources. This should include a historical, political, and organizational assessment to determine who the relevant community leaders are, what community resources exist and which groups and individuals the project should collaborate with. It also includes demographic and epidemiological assessments to accurately identify the community's poor population. Finally, focus groups, interviews, and surveys are needed to determine what the community needs are as seen by the community residents themselves."

Miami and Harlem stressed demographic and epidemiological data to determine the need for an early detection program.

Oakland used community focus groups as well, to determine the perspectives of the community residents themselves as to what the needs were and how best to address them.

"Mistakes were made early when projects identified community leaders who were the wrong leaders. Mistakes were made by failing to identify and work with a real leader who then became a bitter enemy of the project. Each of these types of mistakes are harmful to the project and can usually be avoided by conducting a community assessment."

The third lesson involves the nature of project goals, which should be flexible, community specific, and achievable, Schweitzer continued.

The community itself should be involved in the generation of project goals.

"As it turned out, one of the most fascinating aspects of these projects was their differing goal orientations. Oakland's primary goal is to conduct comprehensive risk assessment and prevention education. Miami's goal is to provide low cost mammography to a large number of poor and underserved women so as to effect a stage shift in the disease, from late to early stage. The Harlem project faces very difficult barriers to access and has shaped its primary goal to confront this reality and thus emphasizes navigation services for cancer patients."

The goals should be practical and achievable, the projects found.

"For example, to reduce cancer mortality is not an achievable or measurable goal for three-year projects, yet these projects were often initially expected to accomplish this."

Keep It Simple

Lesson number four involves planning: Keep it simple; plan for ongoing program evaluation; plan for permanence; plan to avoid turf conflict and resistance to change by clearly defining everyone's role; and plan effective, feasible strategies for cancer control.

Lesson number five: Projects should be multifunctional. Avoid a screening-only approach; always include prevention and education. Each project was dedicated to reaching out to its target population with prevention and education activities. "The purpose of these activities is to combat fatalism, apathy, and myths, the sense that cancer cannot be prevented or that it is an automatic death sentence and thus not worth treating, and to give people a sense of empowerment over their lives," Schweitzer said.

Some of the successful education and prevention strategies learned by the projects are: Hire outreach staff that are indigenous to the community; piggyback onto other community programs agenda so as to address a "captive" audience, such as existing church or community programs; avoid the "cancer only" approach ("For people who do not always know where their next meal is coming from, the relation between diet and cancer may not be particularly relevant. The projects have learned to embed cancer prevention and education issues in larger community issues that are of more immediate relevance for people"); develop materials that are culturally relevant and community specific; keep educational messages simple; fight fatalism by emphasizing a person's ability to affect health through action; emphasize wellness and health, not cancer and fear.

Lesson six: These projects have great potential for professional education, especially for primary care professionals, regarding the value of prevention and of guidelines and procedures for early detection.

Overturning Myths

Lesson number seven: "The belief that poor people are too apathetic to use screening services is a myth," Schweitzer said.

"One of the first challenges leveled at the projects was that they would fail because poor people are too ignorant or too apathetic to use screening services. Harlem, Oakland, Miami, and Atlanta are all urban settings. Their target populations are the urban poor and medically underserved. These groups are usually African American and Hispanic, older, uneducated women who have little or no insurance. Did these projects reach these urban poor populations? In every case they did.

"Overturning the myth that poor urban populations

will not utilize these types of cancer control services, these projects demonstrated that if the services are accessible, available, and delivered in a culturally sensitive, humane and caring manner, the people will come."

Miami used a mobile van to take the mammography screening services to neighborhood primary care clinics where the people were. The project provided approximately 15,000 women with screening mammograms. Forty one percent were African American and 53 percent Hispanic.

The West Oakland project established itself in the West Oakland Primary Care Clinic for primary medical services. The project screened over 2,000 people and provided education and prevention services to approximately 15,000. The people screened were 75 percent women and 83 percent African American.

The Harlem project was located in Harlem Hospital where much of the central Harlem community come for primary care. Eighty four percent of those screened were African American and 11 percent Hispanic.

Lesson number eight: "Don't even think of providing early detection services without ensuring patient followup services," Schweitzer said. To overcome barriers to accessing followup services, each project developed a "patient navigator" or followup role to assist patients. Trained ACS volunteers were used as navigators in some instances. The projects developed computer tracking systems so that they could ensure that followup diagnostic and treatment appointments were scheduled and that the patients kept the appointments.

DCE Board OKs Concepts For New Breast Cancer Grants, Registry

Three new grant supported breast cancer research programs, involving $5.5 million a year for 18 to 22 grants, have received concept approval from the Board of Scientific Counselors of NCI's Div. of Cancer Etiology.

The board also went along with the request for a $2 million a year set aside to fund cooperative agreements for a new collaborative family registry of individuals at high risk for breast cancer which would be used in epidemiologic studies.

None of the three new breast cancer grant programs will definitely go out as RFAs, with set aside funds. If DCE receives its expected share of FY 1994 money earmarked for breast cancer, they will. If not, they will be advertised as program announcements and resulting applications will be competed in the regular R01 grant pool.

The etiology and prevention program will support, with $2.5 million a year, an estimated eight to 10 grants for multidisciplinary research in such areas as endocrinology, anticarcinogenesis and chemoprevention, molecular genetics, cell biology, and metabolism.

The other two--DNA damage, genomic instability and breast cancer; and genetic and phenotypic markers for ionizing radiation induced breast cancer in rodent models and human cells--will involve set aside funds of $2 million and $1 million a year, respectively, each supporting seven to eight and three to four grants. The number of grants and dollar estimates will come into play only if sufficient funds are earmarked to DCE for breast cancer.

At the insistence of board member Maurice Hilleman, the etiology and prevention RFA will also seek studies in retrovirus and indigenous virus involvement in breast cancer. Peter Fischinger, Ru Huang, and Webster Cavenee supported that view. When Chemical and Physical Carcinogenesis Branch Chief David Longfellow commented that "we could use more money" for the add on (the original request was for $2 million a year), DCE Director Richard Adamson suggested another $500,000. The board agreed.

The family registry of high risk persons will appear as an RFA and will be funded through the U01, or cooperative agreement, mechanism. The clinical cooperative groups now supported by NCI for treatment and prevention trials are considered prospective applicants.

The board also gave concept approval to a new RFA for studies of viral interactions with the p53 gene. The $1 million annual set aside would support four to six grants for five years.

Following are excerpts from the concept statements:

[Reports on concept reviews by the boards of scientific counselors of NCI divisions provide advance notice of the Institute's spending plans. Notices of Requests for Proposals, Requests for Applications, or Program Announcements are published in **The Cancer Letter** as they are released; proposals need not be submitted to NCI until that time.]

Breast cancer: Etiology and prevention. Proposed RFA or PA, first year funding $2 million, four years. Program director: David Longfellow, Chemical & Physical Carcinogenesis Branch.

Based on the recommendations of a workshop (Emerging Concepts and Strategies in Breast Cancer, Sept. 5-8, 1990), an RFA is proposed. The objectives are designed to encourage investigator initiated multidisciplinary research on the recommended research questions in the etiology and prevention of breast cancer.

Endocrinology (Hormones/Growth Factors): The role of hormones in etiology and chemoprevention which may affect

neoplastic processes, either by acting alone or in conjunction with nonhormonal chemical carcinogens and inhibitors, should be studied in vitro and in vivo. Endocrine imbalance, namely estrogens and progesterone, is considered highly pertinent in the etiology of breast cancer. The most characteristic property of these hormones is their elicitation of cell proliferation and differentiation in breast tissue. In addition, hormonal interactions with genetic constituents and their receptors, and the modulating effects of chemopreventive agents, should be investigated. Recently, estrogen/progesterone-driven cell proliferation has been proposed as the critical element leading to breast cancer in women. Also of interest is the role in mammary anticarcinogenesis of members of the steroid-tyroid hormone superfamily of nuclear receptors and their ligands (such as retinoids, RARs and RXRs). Further, studies on efficacy and mechanisms of combination chemoprevention of breast cancer, including the use of cytokines, are encouraged.

Anticarcinogenesis/Chemoprevention: Chemoprevention studies are encouraged on the inhibition/suppression of breast cancer in vivo and in vitro, including the use of appropriate sources of human tissue/cell lines. Also of interest are markers of intermediate endpoints as they relate to determining the efficacy of chemopreventive agents. These endpoints may include hormone determinations (estrogen, progesterone, prolactin and other peptides, growth factors and their receptors, estrone metabolites), oncogenes and tumor suppressor genes and their products, and susceptibility genes. A growing number of promising chemopreventive agents for mammary carcinogenesis have been identified in experimental animal model systems, the mechanisms of action for which require detailed investigations (N-acetylcystein, anethole trithione, carbenoxolone, curcumin, fumaric acid, glycyrrhetinic acid, oltipraz). Further, studies are needed on the mechanisms of action of chemoprotective/chemopreventive agents which emphasize the effects on phase I and phase II enzyme systems in breast cancer prevention and that are directed at elucidation of the proximate and ultimate chemical structures responsible for chemoprotection/chemoprevention. Investigations on the role of free radical inhibition in the prevention of breast cancer are also needed. Discovery and chemical identification of naturally occurring inhibitors of mammary carcinogenesis, as well as chemical synthesis and modulation of the structure of compounds, are needed in order to understand structure-activity relationships as a basis for chemoprevention of breast cancer.

Molecular genetics: There is evidence in animal model and human studies that mutations and chromosomal changes are involved in the neoplastic process in breast cancer. It is also evident from studies in colon cancer and other models that multiple changes are necessary for the initiation and progression of normal breast cells to evolve to the final neoplastic and metastatic state. Additional studies are needed to define the molecular events involved in the etiology of breast cancer, to identify molecular markers for each stage in the initiation and progression of the disease, and to identify specific genes and gene products involved in the process. For these studies on the genetics of breast cancer, additional relevant animal and cell culture models may be needed. Transgenic technologies may be especially powerful.

Cell biology: Studies of the organization, proliferation and differentiation of breast tissue, principally primary human mammary epithelial cells, during normal development and progression to malignancy are needed, including studies of the interaction between normal and malignant epithelial cells and the surrounding stroma. Research on the regulation of cell proliferation of primary normal or tumor cells is needed. The differentiating effects of hormones and growth factors on normal mammary epithelial cells from premenopausal women at various physiological states needs to be studied. Guanine nucleotide binding proteins, which are associated with mammary cell growth and differentiation, need to be understood for their role in endocrine tumors of the breast.

Studies are needed to obtain efficient transformation of breast tissue, particularly primary HME cells, to premalignant and malignant cells in vitro and in vivo, emphasizing current concepts of molecular and hormonal carcinogenesis. The specific objectives of such studies are to 1) define in vitro conditions that allow transformation of primary HME cells using chemical and/or physical agents as well as hormones and growth factors, and 2) delineate markers (e.g., biochemical, cytological, histopathological, molecular) that identify specific stages of in vitro and in vivo mammary epithelial transformation and distinguish particular preneoplastic states in the multistep process.

The hormone-mediated growth advantage of early preneoplastic breast lesions, compared to normal breast epithelial tissue at different stages of differentiation, needs to be characterized and the consequences elucidated. Since the development of these preneoplastic breast lesions is likely to be hormonally driven, early estrogen response genes, as well as growth factors and proto-oncogenes, should be examined. Following hormonal exposure, primary animal and human breast cells in culture should be studied and correlated with in vivo data. Aberrant gene expression should be studied initially at the chromosomal level and then at the level of the gene. Gene amplification and suppression, as well as chromosomal abnormalities due to hormonal exposure, should provide important clues to progressive breast cell alterations leading to neoplastic development.

Metabolism: Many polycyclic aromatic hydrocarbons have been established in animals as breast carcinogens. Metabolic activation of PAHs in various tissues is known to proceed by two major mechanisms, one- and two-electron oxidation. The interaction of reactive metabolites with potential target molecules (DNA, RNA, protein) and the relative contribution of the two oxidation pathways in mammary tissue is unknown. Studies also need to be undertaken on which breast tissue P450 isozymes are involved in metabolic activation/detoxification and on enzyme induction itself. Breast tissue from at-risk populations as well as model animals can be used for the detection and quantitation of DNA adducts of these mammary carcinogens in target tissue. Since many of these adducts are not widely available as reference standards, synthesis of adducts is also an area of emphasis which needs to be coordinated with efforts to identify and study markers of exposure and to determine carcinogen dosimetry.

Additional studies on the role of different types of dietary fat in the process of lipid peroxidation, and its effects on the carcinogenic process in breast tissue, are needed.

Several demonstrated rodent mammary carcinogens are present in tobacco smoke. Metabolism of these compounds needs to be examined in human breast tissue/cell lines and compared with other organs; standards are available in the NCI Chemical Carcinogen Reference Standards Repository.

DNA damage, genomic instability and breast cancer. Proposed RFA or PA, first year funding $2 million, four years. Program directors: Raymond Gantt, Radiation Effects Branch, and Paul Okano, Chemical and Physical Carcinogenesis Branch.

Goal of this project is to stimulate research on human breast cancer using molecular, biochemical and cytogenetic techniques to determine whether a genomic instability in nontumorigenic cells is associated with familial breast cancer family members. Suitable cells for this approach might include circulating lymphocytes, normal breast epithelial cells, normal fibroblasts or other appropriate types. Study could include:

1. Determination of the relative capacity of suitable cells from members of breast cancer families to repair DNA damaged by either radiation or chemical carcinogens. Analogous cells from individuals who do not have a family history of cancer would serve as normal controls.

2. Determination of the relative abilities of suitable cells from breast cancer family members to deactivate genotoxic chemicals compared with those from normal controls.

3. Determination of the capacity of suitable cells from breast cancer family members to repair chromosome or chromatid damage from radiation or chemicals compared to those from normal controls.

4. Comparison of the sensitivity of appropriate cells from breast cancer family members and those from normal controls to the initial damage of DNA by radiation or chemicals.

5. Comparison of the relative capacities of suitable cells from breast cancer family members and those from normal controls to maintain the primary sequence of DNA, i.e., replication fidelity, proof reading capacity, prevention of DNA damage and recombination fidelity.

We anticipate that a number of interested investigators will be able to obtain appropriate blood or tissue samples directly from cancer centers and other clinical research oriented institutions and/or indirectly by collaboration.

Genetic and phenotypic markers for ionizing radiation-induced breast cancer in rodent models and human cells. Proposed RFA or PA, first year funding $1 million, four years. Program director: Richard Pelroy, Radiation Effects Branch.

This project will encourage research proposals to study the etiologic and mechanistic basis for the apparent susceptibility of cells in developing breast tissue of human surrogate rodent models to undergo malignant transformation by ionizing radiation. Where feasible, comparative in vitro studies of the effects of ionizing radiation on nonmalignant human mammary epithelial cells also will be encouraged. Following are major objectives:

--to determine the identity of precursor mammary epithelial cells in adolescent female rodents that may be unusually susceptible targets for radiation-induced mammary cancer;

--to determine if there are distinct genes and genetic sequences that are differentially expressed during the progression of finite-span "normal" and immortalized nonmalignant rodent mammary epithelial cell lines to radiation-induced malignancy and if they are etiologic components in the progression of transformed cells to malignancy;

--to assess use, following radiation exposure, of differentially expressed genes, proteins, or mutations during progression as potential biomarkers of preneoplastic lesions for early detection of radiation-induced breast carcinomas in humans.

These objectives suggest that two experimental approaches be explored concurrently: 1) whole animal or organ culture studies and 2) cellular studies in vitro.

Research based upon the use of intact rodent models should include:

1) studies to establish relationships between mammary cells in various stages of developmental maturation (multipotent to mature mammary epithelial cells), their states of functional differentiation (ductal, secretory) and their susceptibility to radiation-induced mammary cancer; and

2) studies that will model the effects of in vivo genetic background (transgenic animals or special strains that express mammalian genes associated with radiation resistance or sensitivity), age, and parity on the susceptibility of pluripotent populations to radiation-induced mammary neoplasia.

Cellular studies: It is important to establish whether precursor-like rodent mammary cell lines undergo the same changes in gene and protein expression during radiation-induced progression to malignancy when they are cultured in vitro as they do in the developing mammary gland. Answers to the following questions might help clarify this issue: i) are the same molecular level changes that are observed in vitro in ionizing radiation transformed finite-life span and immortalized mammary rodent cells also observed in vivo; ii) do such changes in expression of mutational events, genes and gene products follow the same sequence during the progression from the nonmalignant to malignant neoplastic state in rodent cells in vitro and in vivo; and iii) are the same molecular-level changes observed in cultured human breast cell lines as are observed in cultured rodent mammary cell lines during transformation?

These questions might be addressed by research that is directed to:

1) the analyses and functional characterization of DNA sequences that are differentially over or underexpressed during the progression of rodent mammary epithelial cells from a precursor state through immortalized nonmalignant states to cells that form malignant carcinomas in vivo; and

2) studies of the molecular biology that underlie phenotypes that may be associated with radiation-induced breast cancer (alternations in p53 and loss of radiation-induced checkpoints in the cell cycle; the acquisition of growth factor independence for growth in vitro) in relationship to immortalization and progression of rodent and, where feasible, human mammary epithelial cells to malignancy.

Cooperative family registry for epidemiologic studies of breast cancer. Proposed RFA (cooperative agreement), first year funding $2 million, four years. Program coordinator: Daniela Seminara, Epidemiology & Biostatistics Program.

Purpose of this RFA is to stimulate cooperative efforts for the establishment of a comprehensive family registry for epidemiologic and interdisciplinary studies of individuals at high risk for breast cancer. The establishment of population based selection process that could utilize already existing resources, such as SEER or other cancer registries, is strongly encouraged.

The cooperative breast cancer family registry will provide resources to enable participant organizations to identify individuals with a family history of breast cancer, breast-ovarian cancer syndrome, male breast cancer, and various familial syndromes that include breast cancer; collect and

define the related pedigrees; collect clinical (tumor type, stage at diagnosis, hormonal evaluation, etc.), epidemiologic (age at diagnosis, sosciodemographic status, etc.) and other relevant data (such as dietary history) to correlate with the pedigree information. Support for the collection of biological specimens, such as blood samples, paraffin blocks and fresh-frozen tissue will be included. This registry is not intended to directly support research on the mapping and cloning of the gene(s) for breast or breast/ovarian cancer, but to assist investigators funded through other sources by providing the data and biological specimens that can be used for a variety of purposes, including etiologic studies and prevention and treatment-oriented research.

The mechanism of support will be the cooperative agreement (U01). The purpose is to encourage collaborations among several organizations toward the establishment of breast cancer family registries. The collaborative groups will develop common protocols for: ascertainment of breast cancer families; epidemiologic and clinical data collection, validation and management (statistical support); collection and banking of biological specimens (blood and tissues); limited followup for outcome, recurrence and mortality; counseling of family members on risk and possible preventive or therapeutic interventions.

Viral interactions with p53 in human cancer. Proposed RFA, first year funding $1 million, five years. Program director: May Wong, Biological Carcinogenesis Branch.

The goal of this initiative is to stimulate research on the molecular mechanisms by which viral oncogenes from DNA tumor viruses and p53 interact, thereby providing new insight into human tumorigenesis. Examples of studies that may be supported under this RFA include, but are not limited to:

1) Determination of the role of inactivation of p53 and other tumor suppressor genes in human papillomavirus-induced cervical cancer, 2) identification and characterization of viral mechanisms for overcoming apoptosis via p53, 3) determination of the host immune response to altered p53 and how DNA tumor viral proteins affect immune recognition of p53, 4) determination of the possible viral involvement in p53 mutations associated with human breast cancer, 5) identification and characterization of other viral or cellular proteins that physically complex with p53 and whose expression may be modulated by p53, 6) utilization of DNA viruses as probes to study the interacting pathways that are involved in regulating cell growth and to study the function of p53 in inducing growth arrest in response to DNA damage.

DCT Advisors Ok Recompetition Of Drug Development Contracts

Advisors to NCI's Div. of Cancer Treatment have given concept approval to recompetition of contracts for anticancer and anti-HIV preclinical drug development, natural product synthesis, and synthesis of cogeners and prodrugs.

Following are the concept statements:

Preclinical pharmacological studies of antitumor and anti-HIV agents. Recompetition of contracts held by Arthur D. Little, Inc., Mayo Foundation, Southern Research Institute, Univ. of Maryland at Baltimore, M.D. Anderson Cancer Center, and Univ. of Vermont. Estimated $1,218,000 annually (50% cancer; 50% AIDS), five years.

This procurement will provide a continuing resource for conducting defined pharmacology studies of antitumor and anti-HIV agents under development by the Developmental Therapeutics Program.

The preclinical pharmacology contracts will be recompeted at a somewhat lower total level of effort than is currently in place in order to accommodate projected reductions in the DTP contract budget. Although the six current contracts are operating near full capacity, it is anticipated that a more efficient utilization of resources can be obtained by increased integration of pharmacology, toxicology, and efficacy evaluations. Additional emphasis will be placed on determining plasma concentrations at both effective and toxic dose levels and to correlate these findings across species. Correlation of plasma AUCs with the results of in vitro bone marrow studies is also planned. To provide better predictions of the human pharmacology of promising agents prior to clinical trial, the contract statement of work will be expanded to include evaluation of drug metabolism in human liver preparations. In addition, provisions for the conduct of pharmacokinetic studies in nonhuman primates will be added to accommodate the increasing number of immunotoxins, vaccines, and other biological response modifiers selected for preclinical development.

It is anticipated that awards will be made at two levels of effort: Level A--analytical methods development, stability, protein-binding, and pharmacokinetic studies (two routes of administration at two dose levels in one species) with one compound per year (or equivalent effort); Level B--studies as above for two compounds per year (or equivalent effort).

Natural Product Lead-Based Synthesis. Recompetition of contract held by SRI International. Estimated $400,000 annually (50% cancer; 50% AIDS), five years.

The current focus of this contract is on the total synthesis of michellamine B, which has shown activity against HIV-1, HIV-1 (AZT-resistant strain), HIV-1 (the pyridone RT inhibitor strain; A17, Merck and Co.), and HIV-2. Though novel in structure compared with currently known regulators of the AIDS virus, michellamine B has the following drawbacks: an acute supply problem from the natural source, modest potency, limited structure-activity information, and potential for metabolic inactivation. Structurally, michellamine B is composed of a biphenyl backbone and two identical tetrahydroisoquinoline fragments. Because of the urgency for a reliable supply of michellamine B in its natural chiral form, a synthetic strategy through chiral intermediates has been implemented. This will provide useful structure-activity information during the process without extra synthetic effort. With minor modifications, this strategy can be extended to include the synthesis of analogs and congeners with improved physicochemical properties such as lipophilicity and water-solubility. The synthesis is progressing well. A key step in the synthesis, i.e., the coupling of the chiral isoquinoline moiety with an unsubstituted naphthalene, has been achieved under stringent conditions.

It is planned to recompete this contract as a resource devoted to the synthesis and lead optimization of natural

products arising from the Natural Products Drug Discovery Program. The compounds for such synthetic efforts will be chosen from those approved by the Decision Network Committee based on their priority. Emphasis will be placed on either those natural products that are in short supply or those having pharmacokinetic/pharmacodynamic limitations. The contractor will develop both anticancer and anti-AIDS compounds, with the effort approximately equal between the two.

The specific objectives of this program will be:

--Optimization of the biological activity of structurally complex or simpler natural product leads by the design and chemical synthesis of analog series in order to elucidate structure-activity information for these leads.

--Utilization of structure-activity information and molecular modeling as necessary to develop structurally simpler and more readily accessible analogs that may incorporate partial structures.

--Submission of samples of the majority of synthetic intermediates for screening in the primary and secondary antitumor and anti-AIDS assays.

--Design of efficient synthetic routes to lead natural products or their analogs, starting from commercially available intermediates or readily purchased natural products, and execution of these syntheses to provide compounds in amounts sufficient for secondary biological evaluation and further preclinical and clinical development.

Synthesis of Congeners and Prodrugs. Recompetition of contracts held by Univ. of Tennessee, Purdue Research Foundation, Georgia Tech Research Foundation. Estimated $500,000 annually (50% cancer; 50% AIDS), five years.

This project is the recompetition of the current contracts entitled "Synthesis of Congeners and Prodrugs of Anti-AIDS Compounds." The contracts provide a mechanism for carrying out the synthesis of compounds to overcome the shortcomings of such novel but flawed leads, using well-recognized medicinal chemistry strategies.

We propose to continue the effort on congener/prodrug syntheses but at a reduced level, i.e., two contracts instead of three, to develop preclinical candidates and apply design strategies. Mechanism of action studies are anticipated to aid in the design of such candidates. Specifically, one attractive goal could be the chemical modification of sulfated oligo/polysaccharides, which exhibit excellent in vitro activity, are not RT inhibitors, and have very attractive therapeutic indices. Their lack of oral availability has halted their progress toward further clinical evaluation.

To provide greater flexibility, the scope of these contracts will be modified to carry out efforts on either anticancer or anti-HIV leads, in accordance with program priorities.

NCI Advisory Group, Other Cancer Meetings For July, August, September

Bone Marrow Transplantation--July 16, Baltimore, MD. Contact Johns Hopkins Office of Continuing Education, phone 410/955-2959.

Anticancer Drug Discovery & Development Symposium--July 22-24, San Diego, CA. Contact Dr. Frederick Valeriote, Wayne State Univ. School of Medicine, phone 313/745-8252.

Y-ME National Breast Cancer Conference--July 22-23, Chicago, IL. Contact Y-ME, phone 708/799-8332.

Radiation Therapy Oncology Group Semi-Annual Meeting--July 23-25, Philadelphia. Contact Nancy Smith, RTOG, phone 215/574-3205.

Annual Symposium on Cancer Research in San Antonio--July 23, San Antonio, TX. Contact Kathy Johnson, phone 210/677-3850.

Computer Applications for Early Detection and Staging of Cancer--July 28-30, NIH Lister Hill Auditorium Bldg. 38A. Contact Barbara Bonapart, phone 301/496-8544.

Behavioral and Psychosocial Cancer Research--July 30-31, San Diego, CA. Contact Mary LeMahieu, American Cancer Society, phone 404/329-7534.

President's Cancer Panel--July 30, Hyatt Regency La Jolla, San Diego, CA. Open 8:30 a.m.-1 p.m. Topic: Cancer and the Family.

August

Autografting for Chronic Myeloid Leukemia--Aug. 20, Portofino, Italy. Contact Dr. Ann Murphy, AlphaMed Press, 4100 South Kettering Blvd., Dayton, OH 45439.

American Cancer Society National Conference on Breast Cancer--Aug. 26-28, Boston, MA. Contact Andy Cannon, ACS, phone 404/329-7604, fax 404/636-5567.

Oncology Certified Nurse Exam Review--Aug. 27, Dallas, TX. Contact Deb Flanders, program coordinator, Baylor Univ. Medical Center, phone 214/820-2317.

September

Living Fully With Cancer--Sept. 10-11, Houston, TX. Contact Jeff Rasco, MD Anderson Cancer Center, phone 713/792-2222.

Xenogenization of the Cancer Cell: From Basics to the Clinic--Sept. 13-14, Frederick, MD. Contact Margaret Fanning, NCI-Frederick Cancer Research & Development Center, phone 301/846-1089, fax 301/846-5866.

Molecular Mechanisms of Radiation and Chemical Carcinogen-Induced Cell Transformation--Sept. 19-24, Mackinac Island, MI. Contact Dr. J. Justin McCormick, Michigan State Univ., phone 517/353-7785, fax 517/353-9004.

Oncogenes Research and Applications--Sept. 20-22, San Francisco, CA. Contact Cambridge Healthtech Institute, phone 617/487-7989.

Multidrug Resistance and Cancer--Sept. 22-24, San Francisco, CA. Contact Cambridge Healthtech Institute, phone 617/487-7989.

Medical Oncology Board Review Course--Sept. 27-Oct. 1, Houston, TX. Contact Shirley Roy, Conference Services, M.D. Anderson Cancer Center, phone 713/792-2222.

Engineered Vaccines for Cancer & AIDS--Sept. 30-Oct. 2, San Francisco, CA. Contact Cass Jones, phone 619/565-9921.

Future Meetings

Pharmacy Symposium on Cancer Chemotherapy--Oct. 3-5, Houston, TX. Contact Carol Harreld, Conference Services, M.D. Anderson Cancer Center, phone 713/792-2222.

Mechanisms for Cell Growth and Differentiation--Oct. 12-15, Houston, TX. Contact Shirley Roy, Conference Services, M.D. Anderson Cancer Center, phone 713/792-2222.

Ethics and Politics Related to Clinical Trials--Nov. 3-4, Baltimore, MD. Contact conference coordinator, Johns Hopkins Medical Institutions, phone 410/955-2959.