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Healy, Kessler Lose Jobs In Last-Minute Maneuver By Bush White House To Defy Clinton Request

NIH Director Bernadine Healy and FDA Commissioner David Kessler lost their jobs in a last-minute political skirmish between the old and new Administrations last week.

In one of his last acts as President, George Bush refused a request by the Clinton transition team to allow hundreds of senior officials appointed by the President and confirmed by the Senate to remain in their jobs past Jan. 20.

As part of a campaign pledge to renew his Administration, Bush asked

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In Brief

Cancer Center Founder In Bosnia Seeks Attention From Colleagues; Phone Calls Will Help, He Says

A former NCI researcher who founded a cancer center in Bosnia is asking for help from his American colleagues. **Hamza Mujagic**, founding director of Banja Luka Univ. Hospital's oncology program, asked his colleagues to place calls to his home. A large volume of phone calls would tell the Bosnian government that the West is concerned about his safety, Mujagic said in a telephone interview with **The Cancer Letter**.

"If the world knows, the authorities here may pay some attention," he said. Mujagic's home telephone number is (38)78-12525.

Last year, Mujagic ran unsuccessfully for President of Bosnia. Since losing the election, he was fired from his post as chief of oncology at the hospital. Once a regular lecturer at the university, he delivered only one lecture last semester. He said he fears for his safety. Mujagic said he is planning to "make a move" soon, but could not elaborate.

Mujagic said caring for his patients has become nearly impossible. "We can do almost nothing for our patients. The patients really suffer a lot, because in hospitals there is no heat, there is no warm water, and there are no antineoplastic drugs at all."

Mujagic said he is disappointed by what he described as the silence of America's scientists. "They didn't pay any attention to us," he said. "If my former colleagues at NCI published a letter that they are concerned about scientists in Bosnia, that would help."

Mujagic is in regular contact with NCI Div. of Cancer Treatment Director **Bruce Chabner**, who hired him as a visiting scientist for the Clinical Pharmacology Branch in 1980. Mujagic left NCI in 1984, to become a researcher and clinician at Memorial Sloan-Kettering Cancer Center. He returned to Yugoslavia a year later.

Bush Bounces Healy, Kessler In Move To Create Transition Disorder

(Continued from page 1)
for letters of resignation from the so-called PAS employees last October.

Clinton officials said that the traditional practice is for the political appointees to offer their resignations, which would be accepted by the new Administration when replacements are ready.

'Asked Us To Clear The Decks'

But on Jan. 14, a form letter hand delivered from the White House Office of Personnel Management informed Healy, Kessler and about 650 other appointees that their resignations were accepted and their employment expired on Jan. 20.

White House personnel chief Constance Horner said the resignations were accepted "at the request of the Clinton transition team, who asked us to clear the decks of Presidential appointees."

The White House said that if Clinton wanted to keep Bush appointees, he could renominate them and ask the Senate to confirm them again. Or, they could be hired as consultants.

Neither Healy nor Kessler could be reached for comment.

An NIH spokesman, appearing to play down the move, said Healy "resigned and she didn't resign." Healy filed a letter of resignation on Nov. 2 at the request of the White House.

"All that happened is the Bush Administration personnel office notified key presidential appointees confirmed by Senate that resignations were being accepted effective on Inaugural Day," the spokesman said. Before she left, Healy was to designate a deputy to serve as acting director.

Movers were seen packing Healy's office on Jan. 15.

Hoped To Keep Her Job

Since the election, Healy had been lobbying to keep her job. In her Nov. 2 letter to Bush, Healy wrote, "I am hereby submitting my pro forma resignation, but request that it become effective upon the nomination of my successor," according to "The New York Times."

"The pursuit of science is not political," Healy continued. "The NIH has not typically been subject to political shifts that have occurred either in the White House or in the Dept. of Health & Human Services."

Bush officials in HHS were said to be irritated with Healy for seeming to be disloyal to the President who appointed her. In addition, she was rumored to have been considered by Ross Perot as his running mate.

Reaction on the NIH campus last week was mixed. "Some people think she got rid of a lot of deadwood and energized the place, but some of her staff didn't like her," one NCI executive said to **The Cancer Letter.** "The Cancer Institute always got along with her very well."

NCI Director Samuel Broder's job was not affected, since his appointment is not confirmed by the Senate.

Though the new Administration could replace Broder at any time, it appears the Clinton transition, criticized for having only Cabinet secretaries and some White House staff named as of early this week, will have to fill higher posts first.

Broder was out of the country last week and unavailable for comment.

Kessler has been praised by consumer groups and some advocacy groups for reinvigorating the FDA.

A key accomplishment was the passage last fall of legislation requiring user fees on companies that submit new drugs for the agency's approval. The fees will enable the agency to hire more reviewers, promising a faster review time.

RAC Grumbles, Gives Healy Direction She Wants On Urgent Gene Therapy

After several members of the Recombinant DNA Advisory Committee delivered sharply worded attacks on NIH Director Bernadine Healy for approving a protocol for gene therapy for a brain cancer patient, the committee as a whole gave the NIH Director what she wanted:

A set of guidelines that recognized the director's authority to approve one-patient protocols in cases when the severity of a patient's illness allows no time to consult the advisory committee.

The new guidelines in effect state that Healy acted properly in her resolution of the first ever compassionate plea request for gene therapy.

THE CANCER LETTER

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Healy approved the protocol on Dec. 28, without consulting RAC (**The Cancer Letter,** Jan. 15). Shortly after that action, several critics said Healy had caved in to pressure from Sen. Tom Harkin (D-IA), chairman of the Senate Labor, HHS and Education Appropriations Subcommittee, who had written a letter on behalf of the patient.

Addressing the RAC meeting Jan. 14, Healy counterattacked by accusing the advisory committee of demonstrating little "concern for individual patients and their families."

"It is clear... that many of you were uncomfortable with RAC seeming to be put in a position of making a life and death decision," Healy said.

The protocol Healy approved was not on the agenda at the meeting. That matter had been resolved, Healy said.

Instead, the advisors were instructed to formulate broad guidelines for future emergencies, where a patient's desperate condition would leave no time for RAC to consider the treatment protocol at its next scheduled meeting. The committee meets four times a year.

Day Of Criticism

The committee's recommendations followed a day of criticism aimed at both Healy and Ivor Royston, president of the San Diego Regional Cancer Center and the physician whose protocol Healy approved.

After stating her reasons for granting the approval, Healy answered several questions, then left to deal with another pressing matter: the Bush Administration announced it had accepted her resignation.

Healy's approval of the protocol was nothing short of an affront to democracy, said RAC member Gary Chase. "Ultimately, this society rests on the rule of law," said Chase, professor at Johns Hopkins Univ. Dept. of Mental Hygiene. "That is the exceptional ingredient of a democratic republic.

"If the people in power abuse this trust by turning the process of government on its ear in order to accommodate the needs of a single citizen, however desperate that person's plight may be, we and they are ultimately victims," Chase said.

Another RAC member, Abbey Meyers, executive director of the National Organization for Rare Disorders, said that by obtaining compassionate approval from Healy, Royston had in effect evaded review by the committee that had turned down his protocol a year earlier.

Last year, the committee asked for additional data on a multi-patient protocol presented by Royston, but that protocol was different from the one-patient protocol approved by Healy, Royston said.

RAC Defied?

"I know that there has been a lot of sense that somehow RAC has been 'defied' here," said RAC member Nancy Buc, a partner in the New York law firm of Weil, Gotshal and Manges.

"As its name states--not just suggests--RAC is simply an advisory committee to NIH, and in the end, the director is free to do as he or she wishes. In my view, Dr. Healy had the legal authority to do what she did.

"More importantly she had the responsibility to do what she did," Buc said.

In the end, the guidelines formulated by Buc were approved in an 8-3 vote, with one member abstaining.

Under the guidelines, RAC stated that it would henceforth consider one-patient protocols.

Whenever possible, NIH would submit all protocols to review by the advisory committee. However, in emergencies, the Institutes would conduct an internal review.

While conducting an internal review, the director would, to the extent legally and practically possible, consult RAC members as well as experts at NIH and outside the Institutes.

The committee would not distinguish between research and treatment protocols, making both subject to the same safety criteria.

Whenever the director approves a protocol, the details of the decisions as well as the criteria for making it would be presented at the next scheduled RAC meeting.

Healy's Chronology of the Case

Initially, Royston planned to present the scientific rationale for his compassionate plea and the therapy he has begun to administer to his patient.

However, shortly before the Jan. 14 meeting, Royston was informed by NIH officials that his protocol would not be considered by the committee, he said.

It appeared that Healy's strategy was to deal with the legal and political aspects of the case before turning to matters of science.

According to Healy, in October, Harkin asked NIH to "give timely consideration" to compassionate plea requests for gene therapy for the terminally ill. The letter referred to, but did not name, Royston's patient, a native of Iowa.

Harkin's involvement in this case began and ended with the letter, the Senator's staff member said to **The Cancer Letter.** According to the patient's husband, who was present at the RAC meeting, the patient's

sister had worked in a low level job in one of Harkin's campaigns.

"There are no close ties, and no contributions were made," said the patient's husband, who asked that his name not be used and who did not give his name while addressing RAC.

"Since this was the first compassionate plea request for gene therapy received at NIH, and since NIH has no experience or mechanism for addressing such pleas, we thought it imperative for RAC to consider the matter promptly," Healy said.

Thus, Royston was invited to the committee's Dec. 4 meeting. "Although RAC had a lengthy discussion of these issues, it did not provide me with any formal recommendation," Healy said. After asking for RAC's guidance and getting none, Royston wrote to NIH, requesting a compassionate exemption and enclosing an IND application and protocols he had submitted to FDA.

On Dec. 21, Healy suggested that Royston enroll his patient in an NIH protocol.

However, the patient and her family declined to be considered for that study because it would have required another brain surgery just two weeks after her last one, Healy said.

"In contrast, Dr. Royston's protocol was minimally invasive, involving a peripheral injection of cells under the skin," she said.

Vector Approved By RAC, FDA

Several factors made Healy's decision easier.

First, Royston's therapy utilized an approved vector developed by Bernd Gansbacher of Memorial Sloan-Kettering Cancer Center.

That vector was approved by RAC and FDA for melanoma and renal cell carcinoma. FDA decided to view Royston's protocol as an extension of Gansbacher's.

As she was making her decision, Healy did not have to consider the efficacy of Royston's treatment. "Efficacy is not the important consideration," said Bruce Chabner, director of NCI's Div. of Cancer Treatment and one of the NCI officials Healy consulted.

"We deal with compassionate requests all the time, and in many instances there is no information to suggest that the therapy will be effective," Chabner said at the RAC meeting.

Another advisor, Robert Lanman, NIH legal counsel, said that in the absence of mechanisms for compassionate plea exemptions, Healy had the authority to make a decision on Royston's request. Prior approval by FDA was all Healy needed before she could act.

On Dec. 28, FDA approved Royston's request for a one-patient IND and Healy gave her approval the same day.

"Based on this patient's grave condition, a decision had to be made and made immediately," Healy said at the RAC meeting.

"Today I stand by that decision," she said. "First and foremost, the decision was a compassionate response to the request of a dying patient. We took action only after we felt assured that there was no significant risk to either the health of the patient or of the public."

Public Out of the Loop

In discussion that followed Healy's presentation, Donald Krogstad, chairman of the Tulane Univ. Medical School's Dept. of Tropical Medicine, disputed the need for NIH director to act on compassionate pleas.

The process of gearing up for gene therapy takes months, not weeks, Krogstad said. Cells have to be grown and transduced, approvals from FDA and institutional review boards have to be obtained.

All of this gives ample time for physicians to present their protocols at regularly scheduled RAC meetings.

"There should never be a need to do this," said Krogstad, who abstained in the vote on the motion introduced by Buc.

"You are taking the public out of the loop," said Dusty Miller, a RAC member and associate member of the Fred Hutchinson Cancer Research Center Program in Molecular Biology. "The original guidelines are quite adequate."

"Nothing should be approved without review by the RAC," agreed Meyers, of the National Organization for Rare Disorders.

Miller and Meyers voted against the motion, as did Doris Zallen, associate professor of Science Studies and Humanities at the Virginia Polytechnic Institute.

"There Are No Base Motives"

Addressing the committee, Royston acknowledged one error: having assumed that RAC would not consider a single-patient protocol, he did not present his protocol at an earlier meeting.

"In retrospect, I should have submitted the protocol at the December meeting," Royston said.

"There are no base motives," he said. "I am trying to comply with every federal regulation including RAC's.

"We were able to grow the patient's glioblastoma cells. How many people in this country have grown the patients' glioblastoma cells? We were able to

transduce those cells.

"Now the question is, can we help this patient? Is it right for us to treat this patient? Well, absolutely right. Because there are situations where the best available therapy is experimental therapy."

"I am a physician and I am a medical researcher. But when choosing between being a physician and a researcher, I am a physician first. I believe, based on the literature that I have researched and all available data, that there was a strong rationale for providing this patient with this therapy."

Royston is expected to present his data at RAC's next meeting in March.

Mass. Law Requires Reimbursement For Off-Label Use Of Cancer Drugs

Massachusetts Gov. William Weld last week signed a bill requiring reimbursement for off-label use of cancer drugs.

The bill, based on a model legislation developed by the Association of Community Cancer Centers, directs all private insurers to use of the three compendia and peer reviewed medical literature in making reimbursement decisions.

Massachusetts is the fifth state to pass such a law, and the third to do so in recent months.

In a unique provision, the Massachusetts law requires the state insurance commissioner to establish a six-member advisory panel of medical experts to consider reimbursement disputes.

Higher Tobacco Tax May Save Lives, Health Groups Tell Clinton, Congress

Three major voluntary health organizations say Congress and President Clinton should take immediate steps to reduce death and disease caused by tobacco use.

The American Cancer Society, the American Heart Assn., and the American Lung Assn., recommend:

▶Legislation to increase the tobacco excise tax by at least $2 a pack, over the current tax of 24 cents.

▶Legislation to require tobacco products to be fully regulated by the Food & Drug Administration.

▶Comprehensive clean indoor air legislation, including a ban on smoking in the workplace.

The three organizations together form the Coalition on Smoking OR Health. The coalition made the recommendations earlier this month at a news conference in Washington.

"Tobacco use causes more than 434,000 deaths each year in the United States and burdens the national health care system at an estimated cost of $65 billion annual," said Alan Davis, chairman of the coalition and vice president for public issues for ACS.

"What level of moral outrage must be reached before the federal government stops backing down to the tobacco industry and fully commits its resources to fighting tobacco use?" Davis added.

Save 2 Million Lives

The coalition said the tax increase could save 2 million American lives per year. Revenues would raise $35 billion a year which could be used for tobacco use prevention programs and other health programs.

"The only enemy of such a program is the tobacco industry," said Blake Cady, chief of surgical oncology at New England Deaconess Hospital and professor of surgery at Harvard Medical School.

Cady is chairman of the Massachusetts Coalition for a Health Future, which won passage of the state referendum that raised the state's cigarette excise taxes to 51 cents a pack, the highest in the nation.

The coalition's report, "Saving Lives and Raising Revenue: Reasons for Major Increases in State and Federal Tobacco Taxes," is available by contacting the Coalition on Smoking OR Health, 1150 Connecticut Ave. NW Suite 820, Washington, D.C. 20036, phone 202/452-1184, fax 202/452-1417.

Calls For FDA Regulation

The coalition said it is launching an effort to encourage Congress to enact legislation to increase tobacco regulation. Among the specific recommendations:

▶Enactment of federal legislation to require that tobacco products be regulated by FDA as other legal consumer products are regulated including:

--applying the same regulatory standards to the advertising and promotion of tobacco products that are applied to other legal prescription drugs (particularly other nicotine containing drugs),

--requiring that tobacco products are fully labeled to provide the public with additional warnings, full disclosure of additives and constituents, warnings about use with pre-existing medical conditions such as cardiovascular disease, cancer and hypertension.

--prohibiting the use of implied or direct health claims (low tar, low nicotine).

▶Enactment of legislation to prohibit all tobacco advertising and promotion.

▶Enactment of legislation to eliminate the

taxpayer subsidy of tobacco industry advertising and promotion through the business tax deduction.

▶Repeal of the federal preemption on state regulation of tobacco advertising, which limits states' ability to enforce their deceptive acts and practices statutes.

▶Enactment and enforcement of a nationwide or state policy to restrict the distribution of tobacco products to minors including:

--enactment of bans on free sampling, sale of tobacco products through vending machines,

--enforcement of laws setting age restrictions for the sale of tobacco products, including requiring licenses for retail sellers of tobacco products with fines and revocation as a penalty for violation of minimum age laws.

EPA: Cigarette Smoke Is A Carcinogen

Also this month, the Environmental Protection Agency released its report on the dangers of environmental tobacco smoke. The report said secondhand cigarette smoke is a carcinogen which kills about 3,000 U.S. nonsmokers annually because of lung cancer.

The EPA report, begun four years ago, said cigarette smoke has "a serious and substantial public health impact" on nonsmokers, particularly children.

Besides lung cancer, cigarette smoke is responsible for 150,000 to 300,000 cases of bronchitis and pneumonia in young children and increases severity of symptoms in children with asthma.

The report, "Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders," is available by calling EPA's indoor air quality office at 1-800-438-4318, or writing to PO Box 37133, Washington DC 20013, or faxing to 301/588-3408.

NCI Program Announcement

PA-93-39

Title: **Breast cancer in the Northeastern and Middle Atlantic United States**

Despite significant strides in prevention, diagnosis, and treatment, breast cancer continues to be a leading cause of death in the United States. It has been estimated that approximately 46,000 women will die of breast cancer in 1993 and that about 18 percent of all female cancer deaths in the U.S. will be due to malignancies of the breast. The average annual U.S. mortality rate for breast cancer is 27.5 per hundred thousand. Of particular concern are recent data that point to an unexplained increase in breast cancer incidence, and to breast cancer mortality rates that exceed the national average, among women residing in certain of the northeastern and mid-Atlantic states.

In the Report of the Senate Committee on Appropriations, regarding the bill (H.R. 5677) making fiscal year 1993 appropriations for NCI, there was included the following language: "The Committee is concerned by the high breast cancer mortality rates in the northeastern and mid-Atlantic regions of the country and directs the National Cancer Institute to conduct a study with update for four succeeding years for the purpose of determining the factors contributing to the high breast cancer mortality rates in Connecticut, Delaware, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Rhode Island, Vermont and the District of Columbia."

NCI has devoted, and will continue to devote, significant resources to studies of breast cancers. However, not only does a great deal remain to be accomplished so that more effective preventive, diagnostic, and therapeutic modalities can be established, but more emphasis on pertinent basic research is also necessary. This Program Announcement is one of several initiatives that serve to notify and reaffirm to the scientific community the continuing commitment of NCI to expanding research support in basic and applied studies of the etiology, biology and immunology, genetic regulation, diagnosis, treatment, assessment of demographics, patterns of care, and strategies for control and prevention of breast cancer, but specifically to identify, as a matter of the highest Institute priority, the support of such studies as they may apply to populations within the localities identified in the Congressional language cited above. Research under this program announcement also may include data collection, statistical analysis and mathematical modeling, health services research, and information database linkage studies to monitor progress toward cancer control.

Research grant applications may be submitted by domestic and foreign, for-profit and non-profit organizations, public and private. Applications are encouraged from, but not limited to, sites with direct access to the affected populations in the Northeastern United States. Further, the NCI is especially interested in receiving applications from women and from minority investigators.

Support of this program will be through the research project grant (R01) or the First Independent Research Support and Transition (FIRST) award (R29) as well as through competing supplemental awards to currently active research project grants (R01) or Method to Extend Research in Time (MERIT) awards (R37). While there is no limit or cap on the amount of total cost of an individual award under this program, it is anticipated that the average annualized direct cost of awards made under this PA will be approximately $35,000 for competing supplements, $75,000 for FIRST awards and $150,000 for new research project grants. Investigators holding active R01 or R37 grants to study breast cancer or related subjects, with at least one year of support remaining at the time of the anticipated award, or individuals desiring to apply for support under the R01 or R29 mechanisms, are specifically encouraged to apply for grants citing this program announcement.

The purpose of this program is to provide support for investigators to pursue promising avenues of research addressed to breast cancer incidence and mortality occurring in the aforementioned geographical areas. Studies may directly involve populations within this geographical area, e.g., in clinical investigations, or may be concerned with the full range of biological, genetic, environmental, occupational, behavioral or clinical factors that may be relevant to the disease in these

populations.

Topics of interest include:

--studies of whether or not excess mortality can be identified as a direct consequence of excess incidence in these jurisdictions or is due entirely or in part to other factors, such as late stage at diagnosis or problems with access or availability of good quality care;

--delineation of demographic characteristics, including prevalence of personal, family, or socioenvironmental risk factors that could be expected to result in higher than average incidence rates, such as age at menarche, age at first birth, use of exogenous hormones, and/or dietary patterns;

--assessment, through environmental measurements and biochemical analyses, of differences in exposure among appropriate samples of women in areas of low and high breast cancer incidence (e.g., to dietary and nutritional factors, to electromagnetic fields, to toxic substances, especially pesticides, herbicides or contaminants from sewage in drinking water and food); and

--approaches to elucidate racial/ethnic/socioeconomic differences with respect to breast cancer incidence and mortality and the potential role(s) of suspected risk factors, for regions in these jurisdictions having heterogeneous populations.

Interdisciplinary collaborations between geneticists, molecular biologists, epidemiologists, environmental health scientists, public health officials and others are encouraged. While applications will be accepted within any of NCI's relevant extramural program areas as outlined below, the Institute would strongly urge the submission of competing supplemental applications proposing novel projects that represent laboratory-to-clinic transitions in breast cancer or that offer the opportunity for participation of women or underrepresented minority individuals.

NCI is composed of four program Divisions that support extramural research relevant to this program announcement. The spectrum of research supported by these Divisions is as follows:

--**Div. of Cancer Etiology** plans and directs a national program of basic research including laboratory, field, and epidemiologic and biometric research on the cause and natural history of cancer and means for preventing cancer, and evaluates mechanisms of cancer induction and promotion by chemicals, viruses, and environmental agents. **Representative types of research** activities appropriate to this program announcement include, but are not limited to, assessment of the relative contributions and interactions of lifestyle, environment, occupation, genetic factors, viruses, and/or metabolism on the risk of cancers of the breast. In addition, integrated multidisciplinary studies in chemical carcinogenesis are encouraged to identify epithelial cell markers for various stages of transformation, to identify inhibitors of carcinogenesis including natural inhibitors in the human environment, and to determine the specific molecular changes that occur as epithelial cells are transformed.

--**Div. of Cancer Biology, Diagnosis, and Centers** supports research on the cellular and molecular biology of malignant cells, the role of the immune system in tumor growth (including vaccine research) and progression and on the transfer of basic research findings to clinical application for the improved diagnosis/prognosis of cancer. In the area of cancer biology, areas of emphasis include, but are not limited to: soluble factors (e.g., hormones, growth factors), and matrix and membrane macromolecules that modulate the growth of tumor cells; the regulation of the expression of these effectors and the mechanism of action; and the genetic events responsible for progression of tumors to a highly malignant and metastatic state. In the area of cancer immunology, specific interests include, but are not limited to: cellular and humoral immune recognition of tumor antigens, methods of improving immune killing of tumor cells, immune control of tumor metastasis, other regulatory effects of the immune system on tumor growth, and tumor modulation of host immune function. **Studies are specifically solicited** for further research in these areas of immunology aimed at
the eventual development of vaccines for the primary or secondary prevention of these cancers. In the area of cancer diagnosis, areas of emphasis include, but are not limited to: more precise staging of tumors for prognostic and therapeutic decision making, more effective monitoring of response to therapy, earlier detection of both initial and recurrent tumors, and identification of populations at risk for developing particular cancers.

--**Div. of Cancer Prevention and Control** plans, develops, directs, and coordinates research on prevention, control, and community oncology. **Representative studies** involve the identification and evaluation of agents that may inhibit carcinogenesis (initiation, promotion, transformation, and/or progression). These studies could include identification of appropriate agents through literature searches or laboratory methods, efficacy and toxicology studies in animals to aid in selection of materials for human studies, and phase I and II clinical trials of potential preventive agents. Other research could focus on reduction of cancer morbidity and mortality through early detection including
identification of biological markers of risk, exposure, and pre-malignant events of progression. Research on the roles of nutrients, food groups, and other dietary components in cancer incidence is appropriate including the influence of dietary factors on the modulation of cancer risk markers or intermediate endpoints. Cancer control includes research on the development and testing of intervention strategies to modify personal, social, and lifestyle factors known to contribute to the development and/or increased risk of cancer, and multidisciplinary intervention research aimed at addressing minority, underserved, and other special populations.

--**Div. of Cancer Treatment** plans, directs, and coordinates an integrated program of preclinical and clinical cancer treatment research with the objective of curing or controlling cancer in humans by utilizing single or combination treatment modalities. The tumor site addressed by this program announcement currently requires multimodality treatment for optimal management of all stages and presentations of disease, but these treatment methods cause serious morbidity and fail to cure most patients with advanced disease. In preclinical cancer treatment research, there is an urgent need to translate recent developments in the molecular biology of cancer into the discovery of new anticancer treatments whose actions will be highly specific for particular genes or gene products. Exciting areas that may be exploited include oncogenes such as the HER-2/neu oncogene in breast cancer, suppressor genes, signal transduction, cell cycle regulation, growth factors/receptors, metastasis, and angiogenesis. Several approaches will be necessary to take

advantage of these new opportunities. **Additional topics include**, but are not limited to, drug discovery of new anticancer agents, biochemical and molecular mechanisms of antitumor drug action, and pharmacology and toxicology of antitumor agents. Studies to circumvent individual and multiple drug resistance and prevent metastasis of these cancers to other organs are included. Clinical research opportunities exist in the areas of high-dose chemotherapy followed by autologous bone marrow rescue, multidrug resistance, radiosensitizers, adjuvant chemotherapy, innovative surgical or multimodality approaches, particle beam irradiation, novel immune therapies and genetic manipulations of host or malignant tissues, therapy with biological products, such as interleukins, monoclonal antibodies, and/or retinoic acid. Applications that address these opportunities and these particular tumors are specifically solicited.

Inquiries may be directed to: NCI Referral Office, National Cancer Institute, Westwood Building Room 850, Bethesda, MD 20892; phone 301/496-7173; FAX 301/402-0275.

RFPs Available

RFP NIH-NIAID-DAIDS-93-25

Title: Drug development for toxoplasmosis associated with AIDS

Deadline: Approximately March 24

The Development Therapeutics Branch, Basic Research and Development Program, Div. of AIDS of the National Institute of Allergy and Infectious Diseases is soliciting proposals from offerors with the capability to evaluate therapeutic agents for efficacy against Toxoplasma gondii encephalitis and latent toxoplasma infection in a rodent model. The contractor will evaluate therapeutic agents supplied or approved by the Project Officer for efficacy against Toxoplasma gondii in both rodent and in vitro models. During evaluations, the contractor may need to modify, improve or otherwise further characterize the rodent model and or in vitro model or develop other models to improve model utility in the evaluation of therapies. The Contractor may also be required to design alternative protocols and to conduct additional studies for detailed evaluation of promising therapeutic regimens.

Offerors must have in vivo and in vitro models available at the time of proposal. Past experience with animal models for Toxoplasmosis, the availability of the animals and strains of Toxoplasma gondii, and drug testing capability must be documented. This contract will be used to assist in the development of anti-infective therapies, to better understand the potential adverse health effects of such clinical trials.

It is anticipated that one cost-reimbursement contract will be awarded for a five year period of performance.

Direct written inquiries (provide three self-addressed mailing labels) to: Ross Kelley, Contract Management Branch, NIAID, Solar Bldg Rm 3C-07, 6003 Executive Blvd., Bethesda, MD 20892, phone 301/496-2509; FAX 301/402-0972.

RFP NIH-NIADI-DIADS-93-06

Title: Domestic master contract for HIV vaccine efficacy trials

Deadline: Approximately March 19

The Vaccine Trials and Epidemiology Branch, Div. of AIDS, National Institute of Allergy and Infectious Diseases, is soliciting proposals from organizations with the capacity to serve as the Domestic Master Contractor (DMC) for: 1) preparation of sites for efficacy trials and 2) phase III trials of HIV vaccines and other methods for preventing HIV infection in high-risk populations in the U.S. and its territories.

The proposed contract requires expertise in the following areas: coordination and management of multicenter, longitudinal epidemiologic, vaccine, or clinical trials; coordination, training and site monitoring of Phase III vaccine trials; experience with populations at high risk of HIV infection; and solicitation and management of subcontracts. Specifically, the selected contractor will be responsible for the operation and maintenance of a master contract that will provide: 1) subcontracts to sites that are currently conducting baseline epidemiologic studies to ascertain the feasibility of conducting future Phase III HIV vaccine trials; 2) solicitation of proposals from, and monitoring of, additional sites to conduct baseline/feasibility studies; 3) solicitation of proposals from, and monitoring of, sites to conduct Phase III HIV vaccine trials; 4) development of protocols to test HIV vaccines and other biomedical interventions in high-risk seronegative individuals; and 5) an orderly and efficient transition of the proposed contract to a successor, if necessary, at the expiration of the contract.

Inquiries may be directed in writing to: Jacqueline Holden, Contract Management Branch, NIAID, Solar Bldg Rm 3C-07, 6003 Executive Blvd., Bethesda, MD 20892; FAX: 301/402-0972. Requests sent via overnight mail service should use Rockville, MD 20852 instead of the Bethesda zip code.

RFP NIH-NIAID-DAIDS-93-21

Title: International master contract for HIV vaccine efficacy trials

Deadline: Approximately March 19

The Vaccine Trials and Epidemiology Branch, NIAID Div. of AIDS, is soliciting proposals from organizations with the capacity to serve as the International Master Contractor (IMC) for: 1) preparation of sites for efficacy trials, 2) Phase I/II trials, and 3) Phase III trials of HIV vaccines and other methods for preventing HIV infection in high-risk populations in countries outside of the U.S. and its territories.

The proposed contract requires expertise in the following areas: coordination and management of multicenter, longitudinal epidemiologic studies, coordination of Phase I/II and Phase III trials; coordination, training and site monitoring of Phase III vaccine trials; experience with populations at high risk of HIV infection; and solicitation and management of subcontracts. Specifically, the selected contractor will be responsible for the operation and maintenance of a master contract that will provide: 1) subcontracts to sites that are currently conducting baseline epidemiologic studies to ascertain the feasibility of conducting future Phase III HIV vaccine trials; 2) solicitation of proposals from, and monitoring of, additional sites to conduct baseline/feasibility studies; 3) solicitation of proposals from, and monitoring of, sites to conduct Phase I/II and Phase III HIV vaccine trials; 4) development of protocols to test HIV vaccines and other biomedical interventions in high risk seronegative individuals; and 5) an orderly and efficient transition of the proposed contract to a successor, if necessary at the expiration of the contract.

Inquiries may be directed in writing to: Cyndie Cotter, Contract Management Branch, NIAID, Solar Bldg Rm 3C-07, 6003 Executive Blvd, Bethesda, MD 20892; FAX 301/402-0972.