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Healy Comes To Defense Of NCI's Robert Wittes; Official Has Been Target Of Innuendo Over Taxol

Over a year ago, a staff memo to Rep. Ron Wyden (D-OR) referred to a "key NCI administrator" who had gone over to Bristol-Myers, then came back to NCI.

"It is unclear what advantage, if any, this gave to Bristol-Myers in preparing" its Cooperative Research and Development Agreement proposal for development of taxol, the memo said.

Though the NCI official was not named in the memo, it was clear that

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In Brief

James Wallace Named CALGB Executive Officer; Gritz Receives First Joseph Cullen Award

JAMES WALLACE has been named executive officer of the Cancer & Leukemia Group B. Wallace was the group's executive officer when it was based at Roswell Park Cancer Institute; he was chief of medicine at RPCI. Most recently, he served as principal investigator of the Green Mountain Oncology Group Community Clinical Oncology Program in Vermont. Wallace will work in the CALGB central office in Lebanon, NH, one day a week and increase his responsibilities until he is working full time by April 1. . . . **ELLEN GRITZ**, director of the Div. of Cancer Control at the Univ. of California (Los Angeles) Jonsson Comprehensive Cancer Center, received the first **Joseph W. Cullen Memorial Award** at the annual meeting of the American Society of Preventive Oncology, held in Bethesda earlier this year. The new award recognizes distinguished achievement in national tobacco-control efforts through research, development of prevention and cessation programs, or through public policy or advocacy initiatives. Gritz co-authored the 1980 Surgeon General's Report on Women and Smoking and has conducted a wide variety of research in tobacco-related diseases over the past 20 years. . . . . **US TOO**, the prostate cancer support group program of the American Foundation for Urologic Disease, has named **Sen. Bob Dole** (R-KS) and **Sen. Ted Stevens** (R-AK) honorary cochairmen of the group. The senators, recently diagnosed with prostate cancer, are featured in a television public service announcement to be made available to stations in time for Prostate Cancer Awareness Week Sept. 27-Oct. 10. The announcement was funded by Delaware-based ICI Pharma, and offers a toll-free number (800/82-USTOO) for anyone interested in learning more about prostate cancer and support groups. AFUD Executive Director **Arthur Keeney** said the foundation has endorsed US TOO to encourage physicians to begin prostate cancer support groups for patients.

Healy Comes To Defense Of Wittes, Target Of Accusation Over Taxol

(Continued from page 1)

he was Robert Wittes, former head of the Cancer Therapy Evaluation Program who left NCI in December 1988 to become a vice president at Bristol-Myers, then returned to NCI in August 1990 as chief of the Medicine Branch, Clinical Oncology Program (**The Cancer Letter,** Aug. 9, 1991).

Still, a year after this veiled reference in a staff memo, Wittes, who has never been accused of any impropriety or wrongdoing, finds himself in a peculiarly Washington situation: he is being vigorously defended against critics who have failed to demonstrate even a shred of evidence against him.

Following Wyden's staff memo, an article in the May issue of the "Multinational Monitor," a publication started by consumer advocate Ralph Nader, levelled unsupported accusations against Wittes. In July, Wyden cited the article in his query to NIH Director Bernadine Healy. In the most recent development, Healy wrote a detailed defense of Wittes.

Besides portraying Wittes as a skillful administrator who appears to have taken all the necessary precautions to avoid conflict of interest both at NCI and at Bristol, Healy's letter offers a compelling account of history of the development of taxol and Wittes's tenure at Bristol.

In place of hard evidence, Daniel Newman, a research associate with the Center for Study of Responsive Law and the author of the Monitor article, used supposition and quoted accusations.

His section on Wittes began with a qualified j'accuse:

"The giveaway of taxol may have been fostered by Dr. Robert Wittes..."

Then Newman quoted James Love, director of the Washington Taxpayer Assets Project, who characterized Wittes as the "mystery man of the taxol story" and said that "it seems clear that Dr. Wittes gave Bristol-Myers a huge advantage in preparing for the CRADA bid." Love, too, presented no evidence to support these statements.

Newman also wrote that he made several unsuccessful attempts to reach Wittes.

Seizing on the story's publication and Wittes's refusal to be interviewed by the Monitor, Wyden wrote a letter to NIH director Healy.

"The CRADA between NCI and Bristol-Myers has once again been the target of criticism, this time from the journal 'Multinational Monitor,'" Wyden wrote in a letter dated July 15.

"This publication... suggests that Dr. Wittes used his national laboratory position to help the company 'win control' of the taxol development project...

Wyden wrote that Wittes's career history had been detailed for him in a memorandum a year earlier. "We did not pursue this matter, however, based on subsequent assurances from your agency that Wittes had not been in a practical position to assist Bristol-Myers in this potentially lucrative program.

"However, Dr. Wittes's response--or non-response--to queries from the 'Multinational Monitor' rekindles the subcommittee's interest.

"According to the magazine, 'Wittes refused to be interviewed for this article and did not respond to the single written question, 'Did you assist Bristol-Myers Squibb in the preparation of its taxol CRADA proposal?' Bristol-Myers did not return repeated phone calls or answer written questions concerning Wittes."

"Given the positions of high responsibility and knowledge held by Dr. Wittes, and the peculiar timing of his job shifts, I think it is in the public interest to make the record crystal clear on this issue," Wyden wrote.

"We did not go out of our way to bludgeon this guy," Steve Jenning, chief of staff of Wyden's Subcommittee on Regulation, Business Opportunities and Energy of the House Committee on Small Business, said to **The Cancer Letter.** "The last thing we want to be accused of is trying to make hay out of this.

"This is a detailed response and I think they've done their darnedest to answer the questions we posed," said Jenning. "It will also appear that Dr. Wittes has made appropriate decisions to immunize himself against the appearance of conflict of interest."

Is the controversy over?

"We are assessing it," Jenning said.

Wittes declined to comment to **The Cancer Letter.**

THE CANCER LETTER

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Healy's Defense Of Wittes

Following is the excerpted text of Healy's Aug. 13 letter to Wyden:

In your July 15 letter, you express concern regarding the role of an NCI employee, Dr. Robert Wittes, in the development of taxol.

You also mention that you had raised this concern over a year ago, but did not feel the need to pursue the issue after obtaining information from NCI staff.

After careful consideration of the facts, I can assure you that there has been no impropriety or violation of the HHS Standards of Conduct on Dr. Wittes's part.

Dr. Wittes served as Associate Director of the Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment (DCT) from Feb. 14, 1983, until Sept. 6, 1988. In this position, he had broad responsibility for the clinical drug development program of NCI, including all phases of clinical evaluation of promising candidate anti-cancer drugs in the extramural program.

During Dr. Wittes's tenure as Associate Director, CTEP, taxol was one of many candidate agents undergoing clinical evaluation. Interest in taxol increased in the spring of 1988, when researchers from Johns Hopkins reported on its activity in an abstract for the May 1988 meeting of the American Society of Clinical Oncology. The Hopkins data were based on a population of 18 patients in a phase 2 trial of taxol in ovarian cancer. The Hopkins researchers concluded that taxol appeared to be an active agent for treatment of relapsed patients with ovarian cancer. Because of the small size of the treated patient population, the level of activity was uncertain, but the 30 percent response rate was encouraging. At that time, there was no other evidence for activity of taxol in other types of cancer, and no confirmation of the preliminary data in ovarian cancer.

When the data were reported, NCI had a very limited supply of taxol. A working group of NCI staff (which did not include Dr. Wittes) was formed to determine the amount of taxol that might be required for the additional clinical trials to further evaluate this agent.

This group met regularly over the summer of 1988 to develop a strategy for the confirmatory clinical testing of taxol and to project resource requirements.

In early 1988, Bristol-Myers, for their own corporate needs, began a nationwide search for a new vice president to head their cancer research program. In August 1988, Bristol first discussed with Dr. Wittes his possible interest in that position. This recruitment was not an outgrowth of NCI's interest in taxol. After preliminary discussions, Dr. Wittes determined that he had a serious interest in that job and decided to remove himself from further involvement with NCI drug development efforts.

On Sept. 6, 1988, Dr, Wittes was transferred to the temporary position of Acting Deputy Director, DCT, by Dr. Bruce Chabner, thereby shifting him out of CTEP.

Dr. Wittes then relinquished all responsibilities as Associate Director, CTEP, to Dr. Michael Friedman, who was Chief, Clinical Investigations Branch, CTEP.

Dr. Wittes had no responsibilities for CTEP after this reassignment.

In September 1988, the Taxol Working Group (of which Dr. Wittes was not a member) first discussed the need for NCI to enlist the cooperation of a pharmaceutical company to develop taxol further.

Fortunately, the Congress in its wisdom had passed the Federal Technology Transfer Act of 1986, making it possible for federal laboratories to form effective collaborations with private sector organizations for difficult projects, such as the production of taxol. With the advice of NIH legal counsel and the Chief, Office of Technology Development, NCI, it was determined that a Cooperative Research and Development Agreement (CRADA) was the appropriate mechanism for this partnership in accordance with the Federal Technology Transfer Act. Among the key factors in making this decision was the lack of a Government patent position on this drug, and the considerable expense required to identify and develop sources of this compound.

At the time of Dr. Wittes's departure from NCI in December 1988, the use of the CRADA mechanism was under active discussion and consideration by CTEP staff. Dr. Wittes had no role in these discussions, nor in the decision process. In January-February 1989, after Dr. Wittes's departure, CTEP staff requested and received the approval of the Division Director, Dr. Chabner, to prepare the necessary documents and publish an announcement in the Federal Register inviting appropriate private sector organizations to compete for the taxol CRADA.

A Federal Register notice seeking a CRADA partner for taxol was published on Aug. 1, 1989. Proposals were due on Sept. 15, 1989. Only four companies (three from the U.S.) responded. The four proposals were evaluated and prioritized by a panel of DCT staff based on the following criteria, which were published in the Federal Register notice:

--Experience in the development of natural products for clinical use.

--Experience in preclinical and clinical drug development.

--Experience and ability to produce, package, market and distribute pharmaceutical products in the U.S. and to provide the product at a reasonable price.

--Experience in the monitoring, evaluation and interpretation of the data from investigational agent clinical studies under an IND.

--A willingness to cooperate with the PHS in the

collection, evaluation, publication and maintaining of data from clinical trials of investigational agents.

--A willingness to cost share in the development of taxol as outlined above. This includes acquisition of raw material and isolation or synthesis of taxol in adequate amounts as needed for future clinical trials and marketing.

--An agreement to be bound by the HHS rules involving human and animal subjects.

--The aggressiveness of the development plan, including the appropriateness of milestones and deadlines for preclinical and clinical development.

--Provisions for equitable distribution of patent rights to any [future] inventions. Generally the rights of ownership are retained by the organization which is the employer of the inventor, with (1) an irrevocable, nonexclusive, royalty-free license to the Government (when a company employee is the sole inventor) or (2) an exclusive or nonexclusive license to the company on terms that are appropriate (when the Government employee is the sole inventor).

Of the four offerors, only Bristol had significant prior expertise in cancer drug development and clinical testing in this country.

On Dec. 11, 1989, all offerors were notified that BMS had been selected on the basis of the merit of their proposal. Over the next 12 months, negotiations were conducted with BMS and the final CRADA was signed by both parties January 19-23, 1991, The final CRADA includes BMS's agreement to establish a "fair market price" for taxol; this language is now common in NIH CRADAS and usually is referred to as the reasonable price clause.

As a point of special interest, NCI recently signed a similar CRADA with Rhone-Poulenc Rohrer for the development of taxotere. Of course, Dr. Wittes played no role in negotiating the taxotere CRADA.

During the late months of 1989, significant changes were taking place at Bristol that influenced Dr. Wittes's decision whether to remain with the company.

Specifically, in October 1989, Bristol-Myers merged with Squibb Pharmaceuticals resulting in an entirely new organizational structure in its research and development division. Under the reorganization, which was announced in March 1990, the therapeutic-area concept was basically abolished and the individuals who were therapeutic-area directors, such as Dr. Wittes, lost simultaneous control of both preclinical and clinical cancer research and drug development.

Although Dr. Wittes was offered lucrative inducements to remain with BMS, he ultimately decided the job he had originally accepted had changed significantly and he decided to leave BMS in March 1990.

After considering a number of alternatives, including a professorship at Yale (as clinical director of the Yale Cancer Center), Dr. Wittes accepted the position as Chief the Medicine Branch, Clinical Oncology Program, DCT, the position he currently holds.

In this position, he has no extramural responsibilities and is concerned solely with patient care and original research on the NIH campus itself. Please note the timing of these events:

Dr. Wittes returned to NCI in August of 1990, almost a full year after the publication of the Federal Register notice and a full eight months after NCI had notified the other respondents of the selection of BMS for the taxol CRADA.

While employed at BMS, Dr. Wittes was not involved in the CRADA negotiations with NCI. He has not been involved in any way in any of the negotiations with BMS for the taxol CRADA since he rejoined NCI on Aug. 26, 1990.

Upon his return to NCI, Dr. Wittes took the unnecessary precaution of signing a recusal from any dealings with BMS. This recusal was not required because Dr. Wittes had no continuing financial relationship with BMS.

At the time of his return to NCI, Dr. Wittes severed all financial ties with BMS, and has no stock, no stock options, and no pension plan with BMS. As a BMS employee, he did not receive funds from a federal contract or participate in any prohibited activity involving the U.S. government. He did not represent BMS before any government agencies on matters concerning his prior employment in CTEP.

Please note that BMS submitted its proposal in response to the Federal Register notice in September 1989, and was notified in December 1989 of its selection, well before Dr. Wittes's return to NCI. The final CRADA was signed in January 1991.

Dr. Wittes's decision to return to NCI was based on several factors, both personal and professional. He enjoys the challenge of working in our intramural program, and considers the intellectual stimulation worth the loss of salary and other remuneration in the private sector.

In his role as Chief of the Medicine Branch, DCT, Dr. Wittes has no responsibility for the taxol CRADA.

With regard to the article that appeared in the "Multinational Monitor," I must point out that Dr. Wittes was under no obligation to grant the requested interview. His choice to decline to be interviewed should not in any way be construed as grounds for suspicion regarding his conduct vis a vis the taxol CRADA.

This matter has been reviewed by the HHS Office of the Special Counsel for Ethics which concurs that no impropriety or violation of the Standards of Conduct occurred.

In Congress

Some Yew Bark Was Lost In FY91, GAO Finds, But Problems Corrected

A report by the U.S. General Accounting Office found that an unspecified amount of Pacific yew bark had been wasted during collection in fiscal 1991.

According to GAO, neither the Bureau of Land Management nor the Forest Service established the goal of collecting all usable bark. The study was requested by Rep. Ron Wyden (D-OR).

These problems were corrected during the following fiscal year, after Bureau of Land Management and the Forest Service developed stricter harvesting standards, the study found. The Pacific Yew Act, introduced by Wyden and mandating more efficient harvesting of yew on public lands, was signed into law by President Bush Aug. 7.

Bristol-Myers Squibb Co. is decreasing its reliance on trees harvested in the wild, company officials have said. About 4 million yew trees are being raised in nurseries for the company. Also, Bristol has made a deal with an Italian firm to provide a precursor to taxol, 10-desacetylbaccatin III.

GAO found four problems with collection of yew in fiscal 1991:

1. The Forest Service and BLM failed to ensure that yew bark was collected before the sawmill timber was harvested. Yew should be collected before other timber to avoid loss of bark that occurs when the trees are dragged to central collection points or crushed by other felled trees. Both the Forest Service and BLM instructed their field personnel to have the yew bark collected before sawmill timber was harvested whenever doing so was practicable.

2. The equipment used at the time was incapable of removing the bark from logs with diameter of under 4 inches. Moreover, the Forest Service and BLM allowed bark collectors to decide whether all bark that feasibly could be collected had been.

3. Some collection decisions were driven by cost effectiveness of collecting the bark rather than the goal of full utilization. Therefore, usable bark was not always collected from trees that were scattered throughout wide geographical areas.

4. Some yew bark was not collected before the taxol content was lost. A tree has to be processed within 18 months after it is harvested.

The current standards require bark collectors to return to previously harvested sites to recover bark left behind; establish collection priorities requiring that, whenever practical, yew bark be collected before it is destroyed during timber harvesting activities; requires agency field managers to review bark collectors' compliance with the utilization standards, formally document the findings, and notify Bristol-Myers and its bark collectors of any problems.

NIH Scientists May Accept Payment For Nongovernment Activity: OGE

The Office of Government Ethics has issued a final rule that allows NIH career scientists and researchers to receive compensation for teaching, speaking and writing related to their area of expertise, as long as these activities are not directly connected to the employee's specific government responsibilities.

The regulation does not prohibit an employee from accepting payment for "an activity applying the employee's general area of expertise."

For example, an NIH scientist may be paid for "writing or editing a textbook on the treatment of all cancers, provided that the book does not focus on current research at NIH, but rather conveys a scientific knowledge gleaned from the scientific community as a whole." However, the rule would prohibit a scientist from writing a book "which focuses specifically on the research she conducts at NIH."

The "Standards of Ethical Conduct for Employees of the Executive Branch," published in the Aug. 7 "Federal Register," prohibit all career Executive Branch employees from receiving compensation for teaching, speaking and writing about "agency policies, programs and operations, or on specific matters on which they work."

The rule takes effect Feb. 3, and implements an Executive Order signed by President Bush in April 1989 to establish standards of conduct for the Executive Branch.

Proposed Rule For Special Employees Eased

OGE originally proposed that the restrictions on career employees also apply to special government employees such as members of NIH advisory boards and panels.

Members of the National Cancer Advisory Board said the requirements would have made it impossible for most of them to serve; the Board sent a letter of protest to the OGE. In particular, NCAB member Frederick Becker of M.D. Anderson Cancer Center said he would resign and would urge all 220 M.D. Anderson employees serving on advisory boards or committees to resign (**The Cancer Letter,** Oct. 4, 1991).

OGE acknowledged the outcry from the NCAB and

many agencies and organizations, noting that strict requirements would "discourage individuals in the private sector from volunteering to serve."

The final rule prohibits special government employees from receiving compensation for teaching, speaking or writing if the "subject matter deals in significant part with the specific identifiable matter, such as a study or grant, to which the person is assigned."

Also, for employees serving for 60 days or less during the first year or any subsequent year of their appointment, the restriction applies only to "particular matters involving specific parties in which special government employees have participated or are participating personally and substantially."

OGE received 1,068 comments following the publication of the proposed rule last summer.

Defers Decision On Professional Membership

OGE deleted, on the recommendation from the Dept. of Health & Human Services, provisions in the proposed rule that restricted federal employee participation in professional associations, in particular, limiting use of official time to conduct internal affairs of societies. The office said it will issue a new proposed rule covering conditions for professional society participation "at a later date."

The American Society of Clinical Oncology had objected to the proposed rule last year.

The final rule also:

▶ Sets an upper limit of $20 value for gifts that may be accepted by a government employee, with a total of $50 value of gifts that may be accepted in a year.

▶ Maintains the $200 limit on acceptance of awards. HHS had recommended that the limit be lifted to $1,000. Awards above the $200 limit should be reviewed "to ensure that they are given as part of an established awards program," OGE said.

▶ Modifies OGE's position on an employee's use of title in connection with writing. An employee may use his or her title on a written piece if there is a "reasonably prominent disclaimer."

▶ Leaves disciplinary action to the individual agency's discretion.

NIEHS Director Olden Outlines Strategy For Carcinogenicity Testing

The National Institute of Environmental Health Sciences and the National Toxicology Program needs to broaden the scope of its training programs to place greater emphasis on the role of the environment in the etiology of human diseases, the Institute's new director, Kenneth Olden, has said.

Olden, named director of the Institute last year by NIH Director Bernadine Healy, quickly began establishing new goals. Olden, a cancer researcher who at the time of his appointment was serving a term on the National Cancer Advisory Board, outlined his strategy late last year in a symposium at NIH as part of the commemoration of the signing of the National Cancer Act of 1971.

Collectively, the National Cancer Institute and NIEHS have studied 400 environmental substances for carcinogenicity and toxicity in long term animal studies, Olden said; 51 percent of the substances have evidence for carcinogenicity. "This work sets the worldwide standard for toxicological studies and the results provide much of the scientific basis for regulation to protect against human exposure to carcinogens," Olden said.

"Exposure to environmental carcinogens contributes to cancer risk in humans," Olden said. "Classical epidemiology is used as a tool to examine the association between suspected carcinogens and specific cancers in human populations.

"While environmental carcinogenesis is rooted in epidemiology, the assessment of cancer risk has evolved to become a multi-disciplinary science, highly dependent on both in vitro cell systems and laboratory animal studies.

"With the recent advances in cell and molecular biology, we can now begin to assess individual risk. The major limitation in risk assessment is that adequate human data is not available. Also, the validity of interspecies high dose to low dose extrapolations is still a matter of uncertainty.

"Historically, NIEHS has emphasized carcinogenesis as a program priority. Although this emphasis will continue to be an important part of NIEHS, as we look to the future, there is a need to broaden the scope of our research training programs to place greater emphasis on the role of the environment in the etiology of other human diseases and dysfunctions. Some examples include reproductive health, development, neuroendocrine, and immune disorders."

Olden said the Institute's planning will be guided by three principles:

--"Are the results of our studies likely to improve human health?"

--"Do the studies represent an appropriate integration of the traditional environmental health science disciplines of toxicology and epidemiology with the more modern techniques of cell and molecular biology?"

--"Will the studies lead to improvement of risk assessment and development of biomarkers?"

"While it is widely accepted that environmental factors play an important role in the etiology of human diseases and dysfunctions, the causal association has been established for only a few diseases," Olden said. Reasons are: latency, exposure to multiple environmental agents and multiple doses, differences in individual susceptibility, and methods to detect subtle changes lack sensitivity and specificity.

"We intend to exploit both the new tools of basic biomedical research and the explosion of new knowledge to study environmental effects on genes and gene products," he said.

Olden listed some possible areas in which NCI and NIEHS could collaborate:

"One, there is much need for leadership in approving risk assessment. Second, leadership is needed in improving the process for nominating agents for toxicological testing." Olden said he had set up an advisory committee composed of NCI scientists to make some recommendations.

"We could collaborate on research to investigate the effects of UV irradiation, the effects of indoor light, and on the development of biomarkers. We could collaborate to validate the concept of environmental equity. It is apparent that cancer incidence and mortality rates are different depending upon one's socioeconomic status, where one lives, and where one works. It is an issue that we are very much concerned about, and I know the National Cancer Institute is concerned about.

"We could also co-fund some specialized centers. We presently fund 17 Environmental Health Science Centers throughout the U.S. They are focusing on many environmentally related diseases including carcinogenesis."

RFAs Available

RFA AI-92-11

Title: **The effects of silicone on the immune response**

Letter of Intent Receipt Date: Sept. 15

Application Receipt Date: Nov. 20

The Div. of Allergy, Immunology and Transplantation (DAIT) of the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) invite applications for studies focused on the short- and long-term effects of silicone polymers and their breakdown products on the cellular and molecular components of the immune system and its functions and how these changes might contribute to the initiation of self-reactivity and the induction of autoimmune disease.

Applications may be submitted by public and private, foreign and domestic, for-profit and non-profit organizations, public and private. The mechanisms of support for this program will be the research project grant (R01) and the FIRST Award (R29). The total project period may not exceed five years. The earliest anticipated award date will be July 1, 1993.

Up to $650,000 total costs for the first-year, and additional approved expenses for up to five years, has been committed to fund applications submitted in response to this RFA. The NIAID and the NIAMS plan to make approximately three and one awards, respectively, in FY 1993.

Silicone-containing implants and silicone injections have been linked to the development of autoimmune-like diseases, such as scleroderma, arthritis, and dermatomyositis, in some patients. However, there are no solid scientific data to support or rule out the link between the onset of autoimmune disease and the presence of silicone in intact and leaky implants. Furthermore, very limited information is available regarding the effects of silicone administration on the development of normal immune responses and the maintenance of self-tolerance. From the available preliminary information, it appears that some silicone polymers (e.g., D4) have biological activity in vivo similar to Freund's complete adjuvant. Basic research on the effects of silicone in the immune system will be valuable in determining the safety of these devices.

Examples of relevant research topics include, but are not limited to:

--Effects of short- and long-term administration of silicone on the production, structure, and function of lymphocytes.

--Effects of intracellular accumulation of silicone and low molecular weight derivatives in macrophage function, including antigen processing and presentation, cytokine production, and cytotoxic activities.

--Characterization of the profiles and fine specificity of autoantibodies obtained from the sera of patients developing autoimmune-like syndromes who have also received implants.

--Evaluation of the effects of silicone on lymphocyte and monocyte interactions with endothelial cells and fibroblasts and the production and function of adhesion molecules.

--Analysis of silicone effects on the evolution of autoimmune disease in experimental systems, with regard to disease induction, course, and immunologic parameters.

Inquiries may be directed to: Dr. Susana Serrate-Sztein, Chief, Autoimmunity Section, Clinical Immunology Branch, Div. of Allergy, Immunology and Transplantation, National Institute of Allergy and Infectious Diseases, Solar Building, Room 4A20, Bethesda, MD 20892; phone 301/496-7985; fax 301/402-2571; or Dr. Michael Lockshin, Director, Extramural Programs, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Building 31, Room 4C31, Bethesda, MD 20892, phone 301/496-0802.

RFA CA-92-22

Title: **Possible role of metallothionein in carcinogenesis**

Letter of Intent Receipt Date: Oct. 2

Application Receipt Date: Dec. 8

The Chemical and Physical Carcinogenesis Branch in NCI's Div. of Cancer Etiology in collaboration with the Cancer Biology Branch, Div. of Cancer Biology, Diagnosis & Centers, and the Grants and Contracts Operations Branch, Div. of Cancer Treatment, invites investigator-initiated research grant applications to elucidate the possible role of metallothionein (MT) in carcinogenesis. In addition, the National Institute of Environmental Sciences (NIEHS) has an interest in the general topic of metallothionein, but not in the specific emphasis of this RFA, which is the possible role of metallothionein in carcinogenesis. New and experienced investigators may apply for research funds to pursue multidisciplinary research projects.

Applications may be submitted by domestic and foreign,

for-profit and non-profit, public and private organizations. Support of this program will be through the NIH research project grant (R01). The total project period may not exceed four years.

Total costs of $1,500,000 per year for four years will be committed to fund applications submitted in response to this RFA. It is anticipated that 9 to 11 awards will be made contingent upon the availability of funds. The earliest feasible start date will be July 1, 1993.

The objectives of this RFA are to encourage research designed to elucidate the possible role of MT in carcinogenesis. Specific topic areas that might be supported by the RFA include, but are not limited to:

--Biological and toxicological roles of MT. Studies such as metal homeostasis, detoxification, transport, role in cell proliferation during the perinatal period, and involvement of zinc as a second messenger in signal transduction, as related to cellular normality.

--Regulation of MT gene expression. Studies of metal induction in various tissues, during development, and organismal specificity in transgenic and model systems and in normal versus transformed cells.

--Role of MT in tumor cell pathobiology. Studies to define the role of MT in tumor cell progression and metastasis and the types and staging of tumors that may or may not express excess MT. Studies directed at enhancing a rational basis for therapeutic intervention with metallic anticancer drugs.

--Role of MT in cancer chemotherapy. Studies on the role of MT in tumor cell resistance to anticancer drugs, especially metal-based drugs. Studies on the use of induction of MT in non-tumor tissue as an adjunct to reduce toxicity for metallic chemotherapeutics. Studies involving mechanisms by which MT synthesis could be specifically depressed in tumor cells to make them hypersusceptible to metallic chemotherapeutics.

--Susceptibility factors in metal carcinogenesis. Studies assessing MT gene expression in target tissues of metallic carcinogens in rodents and molecular epidemiology of MT with special emphasis on target tissues of metallic carcinogens in humans (e.g. prostate, lung).

--Molecular interaction of MT with ligands (metals and anticancer drugs) including binding and exchange, and structural and dynamic studies.

Inquiries and letter of intent may be directed to: Dr. Yung-Pin Liu, Program Director, Carcinogenesis Mechanisms, Chemical and Physical Carcinogenesis Branch, Div. of Cancer Etiology, NCI, Executive Plaza North Suite 700, Bethesda, MD 20892; phone 301/496-5471, fax 301/496-1040.

RFA CA-92-14

Title: **Biomarkers of dietary fat in post-menopausal women**

Letter of Intent Receipt Date: Oct. 7

Application Receipt Date: Jan. 26

NCI's Div. of Cancer Prevention and Control invites applications for cooperative agreements directed towards the identification and evaluation of potential biochemical/biological markers to assess total dietary fat intake in post-menopausal women and to monitor adherence to dietary interventions
in cancer prevention clinical trials.

The purpose of this RFA is to encourage the submission of applications from qualified investigators interested in conducting investigations designed to identify, characterize, and evaluate biochemical/biological markers to assess dietary intake and adherence. This research initiative also seeks to identify and establish a network of institutions and organizations with scientific expertise, facilities, and capabilities to conduct controlled feeding studies, metabolic studies, and field studies.

Applications may be submitted by domestic and foreign for-profit and non-profit organizations, public and private. This RFA will support awards through the cooperative agreement, an assistance mechanism in which substantial NCI programmatic involvement with the recipient during performance of the planned activity is anticipated.

Approximately $750,000 in total costs per year for three years will be committed to fund applications submitted in response to this RFA. It is anticipated that three to five awards will be made. The total project period may not exceed three years.

The specific objectives of this RFA are to encourage research on the identification and evaluation of biochemical/biological indicators of total dietary fat intake in post-menopausal women on self-selected low- and high-fat diets and in controlled feeding and/or metabolic studies.

A major challenge in studying the effects of diet on health and chronic disease risks is the difficulty of assessing dietary intake. Current methods for dietary assessment and adherence monitoring have different levels of precision and accuracy and all have the inherent limitation of relying on self-reported data. The availability of biochemical/biological markers for assessing dietary fat intake and adherence in post-menopausal women would greatly facilitate the design, conduct, and interpretation of cancer prevention clinical trials, analytical epidemiologic studies, and diet-health survey studies on the relationship of diet and cancer risk. Identification of biochemical/biological indicators of dietary exposure would circumvent the current dietary assessment methodological shortcomings that limit the interpretation of data and often prevent the derivation of precise conclusions about the association of dietary patterns and/or specific dietary components with the risk of cancer and other chronic diseases.

Specific and sensitive biochemical/biological indicators of dietary intake, in particular total dietary fat, would greatly facilitate the design, conduct and interpretation of dietary intervention trials, epidemiologic studies and diet-health survey studies that attempt to determine the role of diet in cancer risk and prevention. In studies involving dietary modifications, the extent to which the results may be influenced by varying degrees of adherence is an aspect that is both important and difficult to evaluate. Thus, evaluation and validation of potential biochemical/biological indices of dietary intake will require controlled human feeding studies using well-defined diets and precise measures of actual intake.

Specifically, applications are solicited that will (1) identify and evaluate potential biochemical/biological indicators of adherence in post-menopausal women on self-selected low- and high-fat diets, and/or (2) identify and evaluate biochemical/biological indicators of adherence to low-fat diets in post-menopausal women in controlled feeding and/or metabolic studies. Applicants may propose also to conduct a series of short-term (6-12 weeks) controlled clinical and/or metabolic studies and/or field studies. These studies should be designed to identify, characterize, and evaluate minimally invasive, specific and sensitive biochemical/biological indicators for assessing total fat intake and/or for monitoring adherence to low-fat diets. Emphasis should be focused on dietary patterns that are nutritionally adequate and are characterized by reduced levels of total fat and saturated fat, increased levels of complex carbohydrates and fiber, and include a variety of foods typically present in the U.S. diet. In addition, the influence of varying the levels of fat intake while keeping fiber intake constant, weight loss, and energy balance may be taken into consideration in the study designs.

Inquires and letter of intent may be directed to: Dr. Carolyn Clifford, Diet and Cancer Branch, Div. of Cancer Prevention and Control, NCI, Executive Plaza North, Room 212, Bethesda, MD 20892-6130, phone 301/496-8573, fax 301/402-0553.