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Fisher Seeks Damages Under Privacy Act; NIH Consents To Remove Database Flags

In a suit filed in federal court, Bernard Fisher demanded that warning flags be removed from medical literature databases operated by NIH and that the government reimburse him for the damage done to his reputation.

Documents filed in the US District Court for the District of Columbia March 6 claim that Fisher's reputation was "attacked and irreparably undermined by the government's world-wide publication of 'electronic graffiti' on ... publicly available computer networks."

The suit claims that the government violated the provisions of the Privacy Act of 1974 when Fisher's publications in NIH-run databases

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In Brief

Heavy Smokers More Resistant To Quitting, NCI Community Intervention Trial Reports

HEAVY SMOKERS were not induced to quit by community-based anti-smoking messages, a $45 million NCI-supported study found. However, light to moderate smokers exposed to the messages had a 3 percent higher quit rate than neighbors who did not participate, according to the results of the Community Intervention Trial for Smoking Cessation, or COMMIT, published in the Feb. 27 issue of the American Journal of Public Health. "It may sound small, but the public health importance of that benefit, if we were to apply it on a national basis, would translate to about 1.1 million fewer smokers," said NCI study director **William Lynn**. NCI *began the trial* four years ago to find out if intense anti-smoking programs would help smokers, particularly heavy smokers, quit. NCI paired 20 demographically similar communities in the US and two in Canada. One in each pair ran the anti-smoking campaign. NCI monitored 10,019 heavy smokers and 10,328 more moderate smokers. At the end of the study, 18 percent of the heavy smokers had quit for at least six months—in both groups. Among smokers of fewer than 25 cigarettes a day, 30.6 percent in the campaign communities quit, compared with 27.5 percent of the control group. "Considering the enormous risks attendant on smoking and the benefits of quitting, such an impact is noteworthy," **Edwin Fisher**, of Washington Univ., wrote in an editorial accompanying the study. Smokers with a high school education or less benefited most from COMMIT's anti-smoking campaigns, Lynn said. Thirty percent of these smokers in the intervention communities kicked the habit, versus 25 percent who didn't hear the anti-smoking messages.

Fisher Suit Claims Privacy Act Violations, Seeks Damages

(Continued from page 1)

were flagged with the words "SCIENTIFIC MISCONDUCT—DATA TO BE REANALYZED."

Fisher was never found guilty of scientific misconduct.

The suit, which seeks damages and attorneys' fees, names *HHS*, NIH, NCI, the National Library of Medicine and the HHS Office of Research Integrity. Also named are NIH Director Harold Varmus, NCI Director Samuel Broder, NLM Director Donald Lindberg, ORI Director Lyle Bivens and HHS Secretary Donna Shalala.

At an emergency hearing March 7, attorneys for Fisher and the US Attorney's office, which represents the defendants, reached an agreement for the entry of a restraining order.

Under the court order, NLM would remove all the tags from the Medline database by March 11. Cancerlit would black out all the flagged entries and keep them off the database while corrections are being made.

Both databases would incorporate corrections that would flash at the time the users log on. The government also agreed notify the medical journals as well as the licensees of the databases.

Judge Ricardo Urbina encouraged both sides to work out a settlement amicably. "It's an interesting case, but I would rather not have to try it," he said in court.

The two sides have till Oct. 26 to work out an agreement.

"The Privacy Act was drafted in anticipation of just this kind of a problem, the problem of inaccurate information about an individual being disclosed and thereby causing harm," said Marc Rotenberg, director of the Washington-based Electronic Privacy Information Center.

"The case is unusual because it seems to be such a flagrant violation," he said.

Rotenberg's group litigates cases that involve electronic privacy issues.

"Any correction by the government will be an apology," said Robert Charrow, Fisher's attorney. "This is the first case I've seen where the problems envisioned by Congress 20 years ago, when the Privacy Act was adopted, have come to pass."

NIH officials declined to comment on the case.

"These developments clearly put Dr. Fisher in the driver's seat with respect to his claims that the decisions from the time of his removal have been arbitrary and the process was mismanaged," said a Washington attorney familiar with the case.

Last month, ORI Director Bivens conceded that the flags on the databases were poorly formulated and directed that the words "scientific misconduct" be removed (**The Cancer Letter**, Feb. 24).

On Feb. 21, in a memorandum, Bivens directed that the words "scientific misconduct" be removed from the flags.

The Fisher suit claims that the defendants altered about 148 electronic records in the NIH-run databases.

"At the time these alterations were made, Fisher was not even under investigation for scientific misconduct," the complaint states.

The complaint cites a press interview in which ORI Director Bivens stated that the investigators' actions in the Fisher case were "unprecedented."

"This is the first case we've had where we put out notification prior to any misconduct finding," Bivens said.

The statement quoted in the complaint was made in an interview with **The Cancer Letter**.

A week later, Bivens said to a reporter that he "misspoke or made an error" when he made the original statement.

"What I said... implied that the flags were put on Medline notices because of the Fisher investigation," Bivens said. "If that is what the reporter heard, I misspoke or made an error.

"It's really based on the [Roger] Poisson confirmed finding of misconduct. It wasn't because of the Fisher investigation or anything we had concluded in the course of that investigation," Bivens

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said (**The Cancer Letter**, March 3).

Bivens elaborated on that statement in a letter to the editor (see page 8).

Poisson is a Montreal surgeon who was found guilty of scientific fraud that included submission of falsified data to the National Surgical Adjuvant Breast & Bowel Project, which Fisher headed.

Fisher's suit claims that:

- The government agencies had wrongfully and illegally disclosed information about the scientific misconduct inquiry involving Fisher. Court documents say it was ORI that directed NCI and NLM to insert the flags in the databases.
- The information disclosed was "false and inaccurate," the complaint states.
- The agencies failed to amend records even after two letters from Fisher's counsel brought the inaccuracies to the attention of the agencies, the complaint states.
- By disclosing information about a pending case, ORI had violated the Administrative Procedures Act. HHS regulations preclude disclosures of information about subjects of any investigation.

Exceptions are made in cases where a significant risk to public health makes such notification essential. Also, when exceptions are made, the respondent must be given notice and a reasonable opportunity to prepare a response.

"Inasmuch as NIH, NCI and ORI waited for over two years after receiving the NSABP reanalysis to annotate Dr. Fisher's records—and during this two-year period prohibited Dr. Fisher from discussing the investigation or the data falsified by Poisson—there was no immediate risk to public health which would justify release of information about Dr. Fisher," the complaint states.

According to the complaint, Fisher was not advised of alteration of his records, the complaint states.

ASCO: Clinician Must Run NCI; NBCC Endorses Geneticist

In a letter to HHS Secretary Donna Shalala, the American Society of Clinical Oncology urged that a scientist-clinician who has a balanced vision of cancer medicine be appointed to the post of NCI director.

While the ASCO letter did not recommend a specific candidate, the National Breast Cancer Coalition took the unusual step of endorsing a candidate, breast cancer researcher Mary-Claire King, of the Univ. of California, Berkeley.

Meanwhile, the search committee led by Paul Marks, president and CEO of Memorial Sloan-Kettering Cancer Center, is aiming to select a candidate before April 1.

Sources said the list of candidates for the position includes Michael Bishop, of the Univ. of California, San Francisco, John Minna, of the Univ. of Texas Southwestern Medical Center, as well as King.

ASCO: Administrator, Good Communicator

In a letter to Shalala dated March 3, Lawrence Shulman, chairman of the ASCO Public Issues Committee, wrote that the NCI director-designee should understand the role of basic, translational and patient-oriented research as part of the Institute's mission. The candidate must also have administrative experience and be an effective communicator, Shulman wrote.

The excerpted text of the ASCO letter follows:

"We believe this is a critical time for NCI and in clinical oncology research, making the selection of the new director particularly important. We urge you to identify a candidate who has the qualities we believe are crucial for carrying out the Institute's goals, including:

"1. The new director should be a scientist/clinician with a broad and balanced vision of cancer medicine, including an understanding of the role of basic, translational, and patient-oriented research as part of the overall mission of the Institute, and the cancer medicine effort throughout the country.

"2. The new director must have already demonstrated administrative capabilities required to lead a large and complex organization such as NCI.

"3. The new director must be an advocate for cancer medicine research who can effectively articulate the needs of researchers, clinicians, and patients to a wide variety of audiences including the lay public, basic and clinical investigators outside of the National Cancer Institute, and Congress.

"This is a very difficult job, presenting tremendous challenges along with great opportunities, and we are hopeful that the new director will succeed. Support of the cancer community is key to the director's ability to make the greatest strides in furthering progress in cancer research and treatment. Your selection of an individual who can meet these criteria will go a long way to assuring the success of the new NCI director and the National Cancer Institute."

NBCC: King Is A Leader, Communicator

The NBCC Board of Directors voted unanimously to support the nomination of King, the coalition wrote in a letter to Stephen Benowitz, NIH human resources director. The letter, dated Feb. 15, was signed by Jane Reese-Coulbourne, NBCC vice president.

The excerpted text of the letter follows:

"We believe Dr. King embodies the criteria described by Secretary Donna Shalala as the future director of the NCI. Dr. King...understands excellence in cancer research. She has served on numerous study sections, boards and national committees that evaluate research proposed by others and set program goals. Her own seminal research in the identification of the location of BRCA1 on chromosome 17 epitomizes research excellence. Following her leadership, prominent investigators from all over the world joined in the race to identify the gene. Most observers would agree that her role in this effort embodies Dr. Shalala's criterion that the next director have the vision to explore new directions in cancer and provide leadership qualities to mobilize researchers to focus on promising new scientific fronts in the basic and clinical arenas.

"Dr. King has also been able to communicate her work and the work of others to individuals of diverse backgrounds; including basic scientists, clinical researchers, health care providers, and consumers alike.... Dr. King is uniquely situated to bring these groups together.

"The National Breast Cancer Coalition has been particularly impressed by Dr. King's personal qualities of integrity and fairness, which we have been able to observe on numerous occasions. She is able to listen carefully to various sides of an argument and come to a conclusion based on the information presented, not based on preconceived notions....

"The combination of Dr. Mary-Claire King's personal integrity, scientific leadership, and ability to communicate effectively with a diverse population make her the best possible candidate for the very important role of director of the National Cancer Institute."

Broder Encourages Support Of Drug Development Program

Weeks away from joining the private sector, NCI Director Samuel Broder recently encouraged the Institute's advisors to support continued funding of the government's anticancer and anti-AIDS drug development programs.

"You frequently hear that certain responsibilities need no longer be assumed by the government, particularly in the area of drug development, or certain kinds of clinical trials," Broder said to the Div. of Cancer Treatment Board of Scientific Counselors last week. "That is extremely uninformed, unintelligent, and will lead to substantial problems in the future."

Broder took a leave of absence on March 1. He is scheduled to resign from NCI on April 1 to take a position as senior vice president, research and development, and chief scientific officer at the Miami-based IVAX Corp.

"There Is No Substitute for DCT"

Broder urged the DCT board to support "the three foundation-stones" of the Institute: cancer centers, clinical trials, and the clinical trials cooperative groups.

"The development of new, interesting, untried, unproven methodologies for intervening against cancer is critical," Broder "There are misunderstandings about what can and cannot be accomplished in the private sector. There is no substitute for the Div. of Cancer Treatment and all of its components."

Broder was director of NCI's Clinical Oncology Program before becoming the Institute director in December 1989.

"All of you, if you believe in this, will need to support the principle that clinical research is a field in the general sense of the term and should be supported and respected," he said. "We need to make sure clinical research is a career that young men and women can undertake with some expectation of success.

"I have not been 100 percent happy with the opportunities provided by our study sections for clinical researchers," Broder said. NCI tried to improve the opportunities through Requests for Applications, he said. "This is an area that needs special attention," Broder said.

NCI programs that help train clinical investigators are also deserving of support, Broder said. "I hope that these kinds of programs which can easily be overlooked in difficult times are protected in some way."

Programs that set NCI apart from other NIH institutes are the cancer centers program, clinical trials and cooperative groups programs, Broder said.

"There is a tendency for uniformity," he said. "There is a tendency to view anything that is unique or unusual as being something that needs to be carefully analyzed. We need to remind everybody in the chain of authority at NIH that the Cancer Institute has unique strengths and unique mission and unique obligations and they have to be protected."

Avoid "Unnecessary Doom and Gloom"

Broder cautioned NCI advisors and staff against becoming discouraged in the coming weeks as the Institute's leadership changes. "As we undertake these difficult times, it is important that we focus on what are the real challenges and avoid unnecessary doom and gloom," he said. "There certainly will be real doom and gloom to deal with."

Basic and clinical researchers must avoid battles over resources, Broder said. "I would caution an unwarranted and artificial combat between individuals who support basic research and clinical research. they are not issues in conflict," he said. "We must do both, and if we plan carefully, we can do both. Both are important.

"We are one Cancer Institute," Broder said.

DCT Advisors Ok $4 Million For Trials Of BRMs

Advisors to the NCI Div. of Cancer Treatment last week gave concept approval to the reissuance of cooperative agreements for clinical trials of biological response modifiers.

The DCT Board of Scientific Counselors approved the set-aside of $1 million per year for four years to fund five cooperative agreement awards.

The board also gave concept approval to four contract programs that support the Biological Response Modifiers Program and the Developmental Therapeutics Program.

Excerpts of the concept statements follow:

Cooperative Agreements for Clinical Trials of Biological Response Modifiers. Reissuance of RFA, five awards, $200,000 per award per year ($1 million total per year, over four years). Biological Response Modifiers Program.

In February 1991 and in June 1992, the BSC approved issuing an RFA to establish cooperative agreements for clinical trials of biological response modifiers. This RFA was initially developed to foster early clinical trials of BRMs or approaches that appeared promising in preclinical studies but had not been tested in the clinic. Applicants were instructed to include evidence of access to the agents proposed for study, evidence that an investigational new drug application (INDA) exists or will soon be filed, and a detailed plan for a pilot clinical trial.

Each past issuance of this RFA has drawn responses (36 applications the first year, 26 the second) from highly qualified investigators. Sixteen awards (seven the first year, nine the second) have been made. The first-year set-aside totaled $1.5 million (total costs). Successful applications have included studies of vaccines (recombinant constructs, cytokine gene-transfected tumor cells, ex vivo pulsing of patient monocyte/macrophages with tumor antigen + cytokine), monoclonal antibodies (bispecific antibodies, humanized antibodies, new radioimmunoconjugates, immuno-toxins), innovative approaches to adoptive immunotherapy, and new uses of cytokines (e.g., to augment autologous graft versus-host disease). All planned clinical trials are derived from the awardee's own preclinical development efforts and include up-to-date approaches to immunologic monitoring, focusing on mechanisms of action. Initial clinical trials are in progress. NCI involvement has included assistance with production or procurement of agents, regulatory advice and support (including NCI holding of the INDA in some cases), assistance with planning of future clinical trials, and plans to chelate monoclonal antibodies for radioimmunotherapy trials.

Because the RFA has succeeded in attracting the types of early clinical development efforts initially sought, BRMP proposes to reissue it, with awards to be made in FY 1996. Reissuance is expected to attract initial applications from investigators who are new to the field of cancer immunotherapy, or who were unable to respond to previous issuances, as well as revised applications from previously unsuccessful investigators and renewal applications from investigators whose original awards will expire in FY 1995 or FY 1996.

Cooperative agreements will be established for the design and execution of peer-reviewed, investigator-initiated clinical trials of BRMs. Each group consists of a principal investigator; one or more laboratory programs with the demonstrated ability to design and perform assays for the monitoring of patients on the study; one or more clinical programs, each headed by a program leader with demonstrated expertise in conducting clinical trials of BRMs; and an NCI coordinator. Applicants shall propose a plan for early clinical development of a BRM agent or approach, adequately supported by their own prior preclinical and, if appropriate, clinical results. The proposal shall include evidence of access to the agents proposed for study, preclinical evaluation indicating that an INDA filing is appropriate, and a detailed plan for a pilot clinical trial. NCI will provide, when appropriate, (1) NCI-supported production of agents at the Monoclonal Antibody/ Recombinant Protein Production Facility, or at contract sites; (2) NCI holding of the IND; (3)

assistance with toxicology testing; (4) assistance with planning and support of a wider range of subsequent clinical trials; and (5) regulatory and technical expertise.

Participation in CATBRMs may include academic, nonprofit, and/or commercial institutions. Application under this RFA may also be a logical step to develop agents arising in NCDDGs, P01s, or R01s.

Collection, Storage, and Distribution of Biological Response Modifiers. Concept for a new RFP, first year award $125,000, five years. Biological Response Modifiers Program.

This contract will provide effective management for the collection, storage, and distribution of materials to peer-reviewed investigators, government laboratories, for-profit institutions, and commercial establishments.

The contractor will be responsible for the receipt, dispensing, shipping, and inventory control of all biological agents distributed through this repository. The contractor must maintain a complete and readily accessible inventory of all materials and shipments. BRMs distributed in bulk amounts include monoclonal antibodies, cytokines, growth factors, and other BRMs and are provided to peer-reviewed investigators for in vitro and in vivo basic research studies. Smaller aliquots of reference reagents include preparations of murine and human cytokines and are provided to peer-reviewed investigators, government laboratories, for-profit institutions, and commercial establishments for use in the calibration of in vitro bioassays and in-house standards only. None of these agents are provided for administration to humans. The contractor must maintain secured, environmentally controlled, and monitored storage areas for all agents, including sufficient 4°C, -20°C and -70°C freezer space. The contractor must also obtain an appropriate Material Transfer Agreement from all investigators prior to the shipping of all bulk materials.

Production, Processing, and Quality Assurance Testing of Biological Response. Concept for a new RFP, first year award $700,000, five years. Biological Response Modifiers Program.

The contractor will be responsible for the production, processing (e.g., purification, vialing), and quality assurance testing of biologic agents. Quality assurance and control testing involves specific assays for sterility, pyrogenicity, endotoxin levels, general safety testing, and preclinical studies related to the development of a safe and efficacious dose and route of administration. The contractor will also be responsible for purification, vialing, labeling, potency, and purity testing of biologics obtained in bulk form for laboratory or clinical use. In some instances production, conjugation, or other modifications of biologics, such as monoclonal antibodies or vaccines for preclinical laboratory use or clinical trials, will also be performed. All procedures will conform to FDA specifications for the development of biologics and will be in compliance with government regulations for human-use products. The contractor will also be responsible for assisting with the development of master drug files and investigational new drug applications on biologics produced by the contractor for NCI.

Synthesis of Congeners and Prodrugs. Recompetition of contracts held by Georgia Tech Research Foundation, Univ. of Tennessee, Purdue Research Foundation, Univ. of Tennessee, Research Foundation of SUNY. Estimated annual amount $851,000 (50% Cancer; 50% AIDS) for 4 contracts, 3 years (with 2 additional 1-year options). Developmental Therapeutics Program.

These contracts provide a mechanism for carrying out the design and synthesis of new compounds to overcome the shortcomings of novel but flawed leads, using recognized medicinal chemistry strategies.

Lead optimization contracts had their inception in 1982 and reached their peak of activity in 1991 with seven contracts: three for anticancer compounds, three for anti-AIDS compounds, and one for natural product-based leads, for a total budget of $1.8 million per year. Five contracts (three for anticancer compounds and two for anti-AIDS) are in operation, all of which will terminate in FY 1996. For greater efficiency and flexibility, we propose to combine the cancer and AIDS contracts.

We propose to continue our lead optimization efforts through the design and synthesis of congeners and prodrugs to develop preclinical candidates. Structure-activity analysis, rapid feed-back of biological data, and mechanism of action studies will be optimally utilized in the development of such candidates. Potential projects include the following:

Cancer: Cosalane and estradiols as anti-angiogenic agents; quinonoid analogs of tyrphostins ("Levitski"-type compounds), and other protein tyrosine kinase inhibitors such as erbstatin; simplified analogs of discorhabdin C and the makaluvamines; tyloindicines, natural products that have been selected by the BEC for in vivo studies, but are unavailable.

AIDS: Simplified tricyclic analogs of calanolide A for synthetic accessibility; semi-synthetic derivatives of michellamine A to improve the therapeutic index; conocurvone (not readily available) and analogs; novel HIV-RT inhibitors; compounds that disrupt zinc finger motifs.

Plant Collections and Taxonomy. Recompetition of contracts held by Missouri Botanical Garden, New York Botanical Garden, and Univ. of Illinois at Chicago. Estimated annual amount $250,000, 3 years (with 2 additional l-year options). Developmental Therapeutics Program.

The number of plant species screened by NCI for antitumor activity to date represents only 10-15% of the estimated 250,000 species available. Of these, an estimated 16,000 species were tested in the earlier NCI program (1960-1981), using in vivo mouse leukemia systems as the primary screen. Even fewer plants have been tested for antiviral activity. In September 1986, 5-year contracts were awarded for the collection of a total of 4,500 plant samples per year from the tropical regions of Africa and Madagascar, Central and South America, and Southeast Asia, respectively. In 1990 these contracts were recompeted, and awards were made to the same organizations in September 1991.

Samples (0.5-1 kg) of different plant parts, such as leaves, bark, stems, and roots, are dried and shipped to the Natural Products Repository in Frederick where they are stored at -20°C. Small samples of each extract are tested for antitumor and anti-HIV activity. When significant activity is observed, bulk extracts are subjected to bioassay-guided fractionation by chemists of the Laboratory of Drug Discovery Research and Development and the active agents are isolated and purified. When necessary, large-scale recollections of active plants are undertaken.

Up to December 1994, 40,264 plant samples had been collected, and 70,664 extracts had been prepared. In 1990, routine testing of extracts in the human cancer cell line screen was initiated using the multidose protocol, but in order to eliminate the significant and growing backlog that had developed versus testing in the anti-HIV screen, it was decided in early 1992 to first prescreen all extracts against the 60 cell lines at a single high dose (100 micrograms per mL). Only those extracts with three or more lines displaying better than total growth inhibition (TGI) (about 20%) are considered for multidose testing. Of these, approximately half are selected for multidose testing, and less than 1 % of the total number of extracts entering the single-dose assay are eventually selected for further investigation. Further selection is determined by comparison of the activity profiles of the active extracts or partially purified fractions with the selectivity patterns of active agents; such comparison may permit the identification of extracts with a particular mode of action (e.g., tubulin binding), as well as the dereplication of known classes of active agents, such as lignins, quassinoids, maytansinoids, etc. Extracts exhibiting unusual activity profiles and/or potent selective cytotoxicity are studied further.

Thus far, 19 plant anticancer projects have been completed, and 10 papers have been published or are 5 being submitted for publication. While none of these plant-derived active agents have been presented for consideration by the DCT Decision Network Committee (DNC), several are under consideration by the DTP Biological Evaluation Committee, including cucurbitacins E and I and the quassinoid, sergiolide. Other active compounds isolated have been novel alkylhydroquinones, cardiac glycosides, cardenolides, chalcones, coumarins, flavones, saponins, and steroidal alkaloids. A number of these classes are being evaluated further; the isolation of the cytotoxic, tubulin-interactive flavone, centaureiden, has prompted a structure-activity study of related flavones, and several saponins are being tested in in vivo models. Eighteen plant extracts are currently in the process of fractionation, and over 200 are on hold, either awaiting fractionation or as lower priority leads. The discovery of relatively few significant new plant anticancer leads to date may be attributed to delays in both the initiation of routine testing of extracts (1990) and the implementation of the high throughput single-dose screen (1992). With these screens now in full operation, it is anticipated that the discovery rate will be significantly improved.

Routine anti-HIV testing of extracts began in 1988, and four compounds have been approved by the DNC and are in various stages of preclinical development as discussed in more detail below. Many common plant metabolites show some degree of activity in the anti-HIV screen. The major recurrent classes of active compounds are polysaccharides, found only in aqueous extracts, and tannins, which occur in both organic and aqueous extracts. Rapid dereplication procedures have been developed for both of these classes, and prior to selection for bioassay-guided fractionation, active extracts are subjected to these procedures. Thus far, 20 anti-HIV plant projects have been completed, and 21 papers have been published or are being submitted for publication. Sixty-five extracts are currently in the process of fractionation, while hundreds are either being dereplicated or are awaiting dereplication prior to being considered for further fractionation.

Of the four plant-derived compounds in preclinical development, the most advanced is michellamine B, a naphthylisoquinoline alkaloid dimer, isolated from a liana (Ancistrocladus korupensis) collected in Cameroon. It shows in vitro activity against HIV-1 and 2 and several drug-resistant strains and is in advanced animal toxicology. Given a favorable toxicity profile, it should advance to clinical trials in mid-1995. The cultivation of the source plant is currently being investigated in Cameroon in collaboration with Cameroon scientists. Calanolide A and costatolide, coumarins isolated from Calophyllum species collected in Sarawak, Malaysia, are reverse transcriptase (RT) inhibitors that act at a different position than nucleoside RT inhibitors. These compounds are being considered as possible candidates for clinical evaluation in combination with existing active compounds, and their large-scale production for advanced preclinical studies is currently under way. Conocurvone is a naphthoquinone trimer, isolated from a Western Australian Conospermum species, that shows potent activity against HIV-1 with a large therapeutic

index. It has been approved at the DN IIA level and is being developed in collaboration with Australian scientists. Prostratin, a 12-deoxyphorbol ester isolated from a Samoan medicinal plant, Homalanthus nutans, is active against HIV-1 and 2 and some drug-resistant strains, and, in contrast to most phorbols, is inactive in tumor-promotion experiments. Nevertheless, the development prospects for this drug remain uncertain.

An additional benefit derived from the collection projects is the distribution of extracts from the Natural Products Repository to qualified organizations for screening against cancer, AIDS and opportunistic infections, and diseases of concern to countries participating in the NCI collections (e.g., malaria). This program started in late 1992, and since then over 12,000 samples have been shipped to 14 approved requestors. Over 300 extracts have shown activity in preliminary screens and are undergoing secondary and/or confirmatory testing. Of the plant extracts distributed, two have shown significant activity against resistant strains of TB, and 26 have shown significant antifungal activity.

There still remain large areas of the world with unique flora that have been little examined, particularly in the regions of rich biological diversity concentrated in the tropics. The availability of these resources is rapidly declining with the destruction of tropical forests by expanding populations. The accomplishments to date clearly demonstrate the potential of plants to produce active agents of interest for the treatment of both cancer and AIDS. These aspects lend an urgency to the continuation of the present program.

Recent developments related to the United Nations Convention on Biological Diversity require that the plant acquisition strategy be substantially revised. Many source countries now require that collections and extractions be performed by their scientists in-country. The following strategy is proposed:

•Two or more contracts be awarded for the continuation of collections in several important countries that presently do not have the capability of performing their own collections on a large-scale (e.g., Madagascar, Papua New Guinea). 1,000 samples per year: $200,000

•One contract be awarded for collections in the United States (possibly including Native American medicinal plants). 1,000 samples per year: $50,000

These collections will be augmented by the acquisition of plant samples or extracts through establishing direct collaborations with qualified organizations in other key source countries.

Agreements are in place or are being negotiated with organizations in Brazil, China, Costa Rica, Ghana, India, Indonesia, Korea, Malaysia, Mexico, Pakistan, Philippines, Russia, South Africa, and Tanzania. The total number of samples to be acquired through this mechanism is about 2,000 per year, and the total number of sample acquisitions will be maintained at the level of earlier years.

Letter to the Editor:

Bivens: No Intent To Link Flags With NSABP Inquiry

To the Editor:

In your Feb. 24 issue, I was quoted as saying that, "This is the first case we've had where we put out a notification prior to any scientific misconduct finding." However, I did not mean to connect the issuance of the Medline and Cancerlit notifications to an ongoing ORI investigation of NSABP.

As stated in my original request to the National Library of Medicine, I asked that a flag be placed in Medline "to indicate that a reanalysis of the [NSABP] study may be needed based on a [June 1993] finding of scientific misconduct on the part of one of the contributors [Dr. Poisson]." The Medline and Cancerlit notifications were predicated solely on the confirmed findings of scientific misconduct by Dr. Poisson, a contributor to the data base underlying anumber of NSABP publications, and were not related to the current NSABP investigation.

Although the current NSABP investigation will examine the data underlying a number of NSABP publications and may therefore generate a fact-base to indicate what publications need reanalysis due to the Poisson misconduct, it is only in this sense that the Poisson and the ongoing NSABP case are related. My comments were not intended to, and should not be construed as, a determination that any authors of NSABP publications, other than Dr. Poisson, have engaged in scientific misconduct.

I did not intend to link the NSABP investigation to the notifications, and to the extent that message was conveyed, it was in error.

Lyle Bivens, Director
Office of Research Integrity

RFA Available

RFA HG-95-003
Title: **Sequence Of The E. Coli Genome**
Letter of Intent Receipt Date: March 24
Application Receipt Date: April 28

The National Center for Human Genome Research invites applications for research projects to complete the genomic DNA sequence of the bacterium Escherichia coli. Total of $2 million will be available. One or more awards will be made.

Inquiries: Robert Strausberg, STB, NCHGR, Bldg 38A Rm 610, 38 Library Dr. MSC 6050, Bethesda, MD 20892-6050, Tel: 301/496-7531, FAX: 301/480-2770, Email: Robert_ Strausberg@nih.gov