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CONTROVERSIAL TOXICOLOGY PROTOCOL IS "GETTING THE INFORMATION WE NEED;" ADDITIONAL REVISIONS MADE

The preclinical toxicology protocol which NCI developed and the Food & Drug Administration approved, with considerable controversy, four years ago has accumulated sufficient experience with drugs subsequently taken into clinical trials to reach certain conclusions,
(Continued to page 2)

In Brief

SARTORELLI REPLACES COLE AS DIRECTOR OF YALE COMPREHENSIVE CENTER; NSABP ENDS SEGMENTAL TRIAL

ALAN SARTORELLI, chairman of the Dept. of Pharmacology at Yale, has been named director of the Yale Comprehensive Cancer Center. Sartorelli, who has been deputy director of the center since 1982, replaces Jack Cole who, the center said in announcing the change, has decided to step down. Sartorelli also heads the center's Developmental Therapeutics Program. Marion Morra, communications manager, has been named to the new position of assistant director of the center. Joseph Bertino, chief of the Section of Medical Oncology, and Sherman Weissman, head of the Molecular Virology Program, will continue in their present positions as the center's associate directors for clinical science and basic science, respectively.... **NATIONAL SURGICAL** Adjuvant Breast & Bowel Project's segmental mastectomy clinical trial has been closed after accruing almost 2,200 patients over more than five years. During the first year, reluctance of surgeons to refer patients to the study almost killed it; before it was over, NSABP Chairman Bernard Fisher felt that segmental mastectomy, or lumpectomy, was being too widely used before results of the study are known. Fisher had called it "the most important clinical trial ever undertaken." Last week he said, "I sometimes exaggerate. But I still think it was the most important one I've ever been involved with, whatever way it comes out".... **NORTHERN CALIFORNIA** Oncology Group is looking for a new executive officer to replace Frank Torti, who has resigned. The job entails coordinating scientific, administrative and planning activities. Those interested should send CVs to Edwin Cadman, Chairman, Search Committee, NCOG, P.O. Box 10144, Palo Alto 94303.... **JOHN POTTER,** director of the Lombardi Cancer Research Center at Georgetown Univ. and a surgical oncologist for nearly 30 years, had this to say in a discussion with the National Cancer Advisory Board on the state of his discipline: "In the last 20 years there has been a decline in the quality of people going into surgical oncology. We have to attract more of the brightest students. My personal bias is that there will be improvement in surgical oncology only when there is certification of competence or some similar method."

DCT Board Sends Message On Cutting Grants To Extend Paylines, Then Tries To Take It Back
. . . Page 7

NTP Carcinogenesis Testing/Evaluation Panel Finishes Draft Of Report
. . . Page 3

St. Jude Offers Three Fellowships
. . . Page 6

NCI Test Panels Available For Marker Evaluation
. . . Page 6

RFPs Available
. . . Page 8

NEW TOXICOLOGY PROTOCOL CUTS COSTS, REVISED TO ADD RAT TOXICITY STUDY

(Continued from page 1)

the Div. of Cancer Treatment's Developmental Therapeutics Program has reported to the division's Board of Scientific Counselors.

The new protocol, which cut the cost of toxicology studies by almost half and shaved several months off the time required to get a new drug into clinical studies, eliminated tests in monkeys, decreased studies in dogs and increased testing in mice. The protocol was drawn up by NCI staff with the help of consultants, was approved by the DCT Board and by FDA's Oncologic Drugs Advisory Committee, both after extensive discussion, but still aroused opposition on the part of some FDA staff members. One, Robert S.K. Young, carried his opposition so far as to file a citizen's complaint with the FDA commissioner (which was rejected), and Young eventually gave up his position as group leader in the Div. of Oncologic & Radiopharmaceutical Drugs as a result of the controversy. Young remains as a medical officer with FDA.

Charles Grieshaber, chief of the Toxicology Branch in the Developmental Therapeutics Program, reported to the Board of Scientific Counselors that conclusions made from quantitative toxicology experience with the first seven drugs taken into clinical trials after going through the new protocol were:

1. The mouse tests provided safe human starting doses.

2. Toxicity data from the beagle dog has little utility in predicting whether the starting dose represents a hazard to humans. In three cases where data on the dog indicated that the starting dose should be lowered to a smaller fraction of the starting dose determined in the mouse studies, there was little or no human toxicity noted upon escalation to the mouse-indicated dose. In the case of one drug, fludarabine, the safe entry level dose should have been less than that indicated in the mouse study, but data from the dog did not so indicate.

3. Escalation procedures cannot be efficiently predicted from currently acquired preclinical information. (DCT is undertaking a new effort to address this problem—see below.)

The seven drugs are NMF, CBDCA, teroxirone, homoharringtonine, DHAC, FAMP, and fludarabine.

"From our experience with seven drugs which completed both preclinical testing and phase 1 clinical trials, we can say that mouse lethality data . . . provides a safe starting dose for humans in six of seven cases," Grieshaber said. "Toxicity studies in dogs were effective in disclosing human dose limiting toxicity and approximated the maximum tolerated dose for six of the seven drugs. However, dog data was ineffective in discerning the relative safety of estimated human starting doses. In the exceptional case, fludarabine, the dose level for human toxicity was grossly underestimated in both experimental species."

The new protocol used mice for both lethality and optional (in addition to the dog) toxicity studies. However, it was found that evaluation of hematology and clinical chemistry data indicated that platlet counts, total whole blood counts, neutrophils, lympocytes, and BUN, SCOT and SGPT values were widely variable in nontreated control mice. "Thus, these highly variable parameters did not serve as consistently useful indicators of toxicity in drug treated mice," Grieshaber said. In discussions with FDA, it was recommended and approved that the optional toxicity studies be carried out in the rat rather than the mouse. That protocol now is currently in use—lethality studies in mice and acute toxicity studies in dogs, with the Fisher 344 rat substitutded as the rodent species for the optional acute toxicity studies.

"In light of our evaluations, the dog serves better as a prognosticator for organ toxicity in humans than the mouse," Grieshaber said. "We must await completion of ongoing preclinical toxicology studies and clinical trials to ascertain whether the rat serves as well or better than the dog for this purpose."

"This is really a status report," DCT Director Bruce Chabner said. "This is a shorter protocol, and it gets toxicology information at less cost. We believe we are getting the information we need for safe starting doses, except for fludarabine. I don't understand that. It is probably a matter of pharmacokinetics. With more tests, we may have the answer in two years. In general, we are underpredicting safe starting doses, and that causes more escalations and costs."

David Richman, FDA pharmacologist who was one of those who had serious misgivings about the new protocol in 1980-81, was at the meeting when Grieshaber made his report. Later, he told **The Cancer Letter** that much of his original objection was based on the contention that the protocol would not predict for organ toxicity. "It still doesn't," he said, as Grieshaber's report acknowledges. Adding the rat acute toxicity studies may help, Richman said.

Richman emphasized that he supports the statement made by former FDA Bureau of Drugs Director Richard Crout (now head of the NIH Office for Medical Applications of Research) which Crout made at the annual meeting of the American Society of Clinical Oncology in 1982 in discussing the new protocol:

"The primary intent of animal testing under the new guidelines is to estimate a safe initial dose for the beginning of phase 1 trials," Crout had said. "It is not to establish the organ toxicity of the drug, the usual objective in most toxicologic work. The strategy adopted by the guidelines is that, regardless of the findings in animals, potential toxicity to any organ must be presumed for this highly toxic class of drugs and be specifically sought in humans. The burden for identifying and limiting organ toxicity in patients has, of course, always rested with those who study these agents in clinical trials and use them in the care of patients. The strategy followed in the new guidelines makes that burden explicit. . . I would emphasize to this audience that those of you who conduct clinical trials of cancer drugs have a critically important role in determining the success of this new toxicologic approach."

DCT has initiated an effort to reduce the number of dose escalations needed in phase 1 clinical studies through use of pharmacologic measurements.

Jerry Collins, chief of the Pharmacokinetics Section of the Clinical Pharmacology Branch in DCT's Clinical Oncology Program, described the project and its rationale at the DCT Board meeting:

"The starting dose for a phase 1 clinical trial of a new anticancer drug is determined primarily from preclinical toxicologic studies in mice. Although there is always therapeutic intent, the principal objective of a phase 1 trial is to determine the maximum tolerated dose which will be used to establish the dose for more detailed efficacy studies (phase 2). Once the starting dose has been evaluated, subsequent doses are escalated until the MTD is reached. The rate of escalation is defined empirically by a modified Fibonacci series. The initial escalations are rapid (doubling the dose), but subsequent escalation steps are reduced to 25-30 percent increases. This universal escalation scheme is applied to all drugs, with no modifications based upon pharmacology or other factors.

"If the starting dose is far removed from the MTD, a large number of dose escalations is required. Consequently, most patients receive subtherapeutic doses and the amount of resources allocated to each drug increases. The Blood Level Working Group is a new initiative of DCT which is charged with the responsibility of investigating the use of pharmacologic measurements to improve the efficiency of the phase 1 testing process. Clinical pharmacokinetic measurements are already part of many phase 1 trials and preclinical pharmacokinetic data can be obtained when needed. We are exploring potential strategies for controlling the rate of dose escalation based upon pharmacokinetic determinations in mouse and man. Retrospective analyses indicate that 20-50 percent savings in the total number of dose escalations are possible.

"To make this project practicable, enhanced coordination of extramural resources between the Developmental Therapeutics Program and the Cancer Therapy Evaluation Program has been established. Preclinical pharmacology task orders have been utilized to develop reliable assay methods and pharmacokinetic data in mice. This information will be obtained in parallel with final toxicologic testing, and will be available at the time clinical trials begin. New clinical phase 1-2 contracts are being restructured to provide clinical pharmacokinetic data as soon as the first patients are treated, and to provide the mechanism for dose escalation based upon pharmacologic measurements.

"Intramural laboratories in DTP and the Clinical Oncology Program are also coordinating their efforts with the Blood Level Working Group in the areas of drug assay and pharmacology studies in mouse and man."

"It is refreshing to see you move away from empiracy for drugs moving into clinical trials," Board member David Goldman said.

"The problem we had a few years ago about drug toxicity in the press was the charge that so many patients were not receiving any benefit in phase 1 studies," Chabner said. "With this effort, we can move more rapidly in escalating doses, which could improve that situation."

CARCINOGENESIS TESTING/EVALUATION PANEL FINISHES DRAFT OF REPORT

The National Toxicology Program should continue to develop and improve short term tests for chemical carcinogensis, the ad hoc Panel on Chemical Carcinogenesis Testing and Evaluation recommended in its draft report, now available for comment. The panel also offered recommendations for using and improving subchronic and chronic studies, developed in deliberations of four subgroups after NTP's Board of Scientific Counselors determined a year ago that a review of the basic biology and chemistry of chemical carcinogensis was needed with the goal of recommending methods NTP should use in detection and evaluation of chemical carcinogens.

Copies of the draft report are available from the panel secretary, Janet Riley, P.O. Box 12233, Research Triangle Park, N.C. 27709. Comments on the report may be submitted to the same address and should be in by March 30. A shorter version of the report also is available.

A summary of the panel's recommendations follows:

Short Term Tests

1. The National Toxicology Program provides a unique resource for validating short term tests and

in particular for obtaining complementary and parallel data on tests in vitro and in vivo in animals and humans. This resource needs to be developed and utilized.

2. NTP should carry out studies on levels of mutagenic material in blood and urine from selected animals in the prechronic test to provide information on the quantitative relationships between carcinogen intake and mutagenicity of blood and urine.

3. NTP should introduce into its program studies on covalent adduct formation in animals treated with chemicals under the carefully controlled conditions of the bioassay protocol.

4. The rat hepatocyte UDS test using metabolically competent cells should remain on NTP's standard battery of short term tests. Chemicals of specific classes known to require metabolism by the intestinal microflora should be tested in the in vivo/in vitro test. In addition, when a chemical induces hepatocellular tumors in the bioassay, but was negative in the in vitro hepatocyte UDS test, it should be tested in the in vivo/in vitro test.

5. The micronucleus test should be included as a secondary or tertiary screen in the NTP gene-tox battery.

6. NTP should support the development of automated methods for gene-tox assays. The micronucleus test, for example, would then be available as a routine assay.

7. NTP should continue to employ the SCE in vitro assay using Chinese hamster ovary (CHO) cells in the NTP standard battery of short term tests.

8. NTP should include an assay for SCEs in the proposed in vivo test scheme.

9. The use of the lymphocyte assay for chromosomal abberations is recommended for parallel testing in in vitro systems, in laboratory animals and in humans. NTP should retain the CHO in vitro study in its genetic toxicity prechronic battery and should include chromosomal aberrations among the short term tests applied in the proposed in vivo animal study of model compounds.

10. Somatic cell mutation tests such as the mutant hemoglobin assay, the glycophorin assay, and the specific locus mutation assay in T-lymphocytes should be further developed and validated. At some future time they could be considered for inclusion into either the NTP standard battery of short term tests or into the proposed in vivo testing scheme.

11. The mouse sperm morphology assay should be used in a selective manner in the NTP prechronic testing, specifically for those chemicals whose chemical structures indicate that they may be potent carcinogens or be active on male germ cells. The assay should be considered for inclusion into the proposed in vivo test scheme. Further validation and evaluation as a predictor of carcinogenicity is needed.

12. Since short term tests for transformation and promotion extend the range of any short term test battery, these areas should be given emphasis in the NTP test development and validation program.

13. NTP should conduct laboratory animal studies using model compounds to validate selected in vivo short term tests as indicators of internal activated dose, biologically effective dose or preclinical genetic response. Potential cooperative studies with other agencies having access to human material would permit possible comparison and collaboration of human responses with the animal data.

14. NTP should consider storing biological fluids from animals in certain bioassays to be used retrospectively in newly developed assays.

15. NTP should attempt to understand discrepancies between short term test data and chronic bioassays by developing more complex in vitro systems. Such sophisticated tests could also lead to an understanding of mechanisms.

16. NTP should give greater weight to positive short term test data than to negative data.

Subchronic Studies

1. NTP should develop definitive criteria for each of the elements used in the chemical selection process.

2. Where possible, the exposure factor should be used in the selection process in view of its value in subsequent risk assessments.

3. NTP and the Board of Scientific Counselors should explore the possibility of external peer review of the decisions made between the prechronic test and the chronic bioassay.

4. NTP should for the present continue to use the Fischer 344 rat and the B6C3F1 mouse in the bioassay. However, efforts should be devoted to determine whether both species are needed for detection of carcinogens.

5. If two species are maintained in the future, NTP should consider replacing the B6C3F1 mouse with a strain having lower and less variable incidence of spontaneous tumors at sites also induced by chemical agents.

6. NTP should continue to develop formal methodologies employing toxicological, pharmacological and other relevant experimental data as well as human exposure estimates in selecting doses for the carcinogenesis bioassay.

7. Pharmacokinetic studies, if employed, should be performed before or during the prechronic tests so that as complete a data set as possible will be available for design for the chronic bioassay.

8. The route chosen in the bioassay should reflect the predominant human exposure route to the extent possible for a valid assay. Where alternate

routes are selected, the rationale should be supported by appropriate pharmacokinetic, toxico-

porates contemporary quality assurance and good laboratory practices.

15. NTP should further develop the criteria for carcinogenicity in experimental animals and establish a list of noncarcinogenic substances for reference use by the scientific community.

16. Where a specific study suggests progression from benign to malignant neoplasms in a given organ, the incidence data may be combined to aid in the evaluation of the response.

17. Neoplasms of the same histomorphogenic type may be combined even if they occur in different anatomic sites. Similarly, neoplasms of different morphologic classification may be combined when their histomorphogenesis is comparable. In practice, the evaluations should be made separately and later combined for possible clarification of the response.

18. NTP should continue to evolve a system for classifying the findings of a bioassay (by sex and species) with regard to strength of the experimental evidence supporting the conclusion of carcinogenicity or noncarcinogenicity.

19. Every bioassay report should contain a clear statement of the purpose of the study.

Regulatory Decision Making

1. Because of its value not only scientifically but also for regulatory needs, NTP should provide guidelines and principles whereby the results of a bioassay can be attributed to the test agent or to confounding factors. This process is aided by documented adherence to good laboratory practice and comparable guidelines.

2. NTP should assess the effect of modifications and enhancements in the bioassay process on the validity of results of earlier assays.

John Doull, chairman of the Dept. of Pharmacology and Toxicology at the Univ. of Kansas, was chairman of the ad hoc panel. Other members were Richard Adamson, director of NCI's Div. of Cancer Etiology; Perry Gehring, Dow Chemical Co.; Richard Griesemer, Oak Ridge National Laboratory; Kim Hooper, California Dept. of Health; Sanford Miller, FDA; Riggero Montesano, International Agency for Research on Cancer; Ian Munro, Canadian Center for Toxicology; Frederica Perera, Natural Resources Defense Council; Robert Scala, Exxon Corp.; Andrew Sivak, Arthur D. Little Inc.; Bernard Weinstein, Columbia Univ.; and Gerald Wogan, Massachusetts Institute of Technology. In addition, NTP Board members Norman Breslow, Henry Pitot, and James Swenberg served on the panel.

ST. JUDE OFFERS THREE FELLOWSHIP PROGRAMS FOR PHYSICIAN-INVESTIGATORS

Three fellowships are offered by St. Jude Children's Research Hospital each year, with an application deadline of Sept. 1 and award date starting the following July 1.

The Levy Fellowship in Cancer Medicine is available to a physician investigator planning a career in cancer medicine. Levy fellows train in one of the specialty areas of research emphasized at St. Jude—hematologic malignancies, pediatric oncology, infectious diseases, nutrition, cancer pathology, human tumor cell biology, biochemistry, immunology, pharmacology, virology, and molecular biology. Awards are made for two years with an additional year negotiable.

The Journey Fellowship in Biomedical Research is open to a junior investigator with an MD or PhD who seeks experience in one of the specialty areas of research available at St. Jude (listed above). They are made for one or two years with an additional year negotiable.

The Karnofsky Fellowship in Cancer Research is available to investigators with either a PhD or MD who are beyond the junior level of accomplishment and would like to gain further expertise in cancer research by collaborating with a member of the St. Jude faculty. Research topics currently under investigation include drug resistance, oncogenes, hematopoietic stem cell differentiation, red cell aging, cancer clinical trials, oncopathology, monoclonal antibodies, and experimental marrow transplantation.

Those interested may contact Dr. Joseph Simone, Director, St. Jude Children's Research Hospital, P.O. Box 318, Memphis 38101, phone 901-522-0300.

TEST PANELS AVAILABLE FOR EVALUATING BIOLOGICAL MARKERS FOR BREAST CANCER

A bank of serum specimens from women at varying risks of breast cancer has been established in the Diagnosis Branch, Div. of Cancer Biology & Diagnosis, of NCI. Panels of test specimens are available to investigators to evaluate newly discovered biological markers for breast cancer, to verify preliminary data and to study multiple markers for early detection of breast cancer. Sera are maintained at -70 degrees C in 1 ml sealed glass vials.

Requests for test panels must document the discriminatory power of their assays. The serum bank cannot support feasibility studies based on theoretical considerations nor can it handle large population based epidemiological studies. The assays must not require more than 1 ml of serum for accurate determination. Requestors must agree to accept specimens under a blind code number and report the results to NCI. Some duplicates will be included in each test panel.

To request a test panel, write a letter addressing the above points to Dr. I.J. Masnyk, NCI,DCBD, Bldg 31 Rm 3A04, Bethesda, Md. 20205.

DCT BOARD SENDS MESSAGE ON GRANTS FUNDING, THEN TRIES TO TAKE IT BACK

The Board of Scientific Counselors of NCI's Div. of Cancer Treatment first went on record at its recent meeting favoring what NCI calls a "funding plan"—that is, reducing grant awards by a certain percentage in order to increase the number of grants which can be funded. That had been NCI's practice during the past few years in dealing with virtually level budgets. But the Board later indicated that it may not feel all that strongly about the issue.

Congress in making the FY 1984 appropriations decreed that grants should be funded at or near their peer review recommended levels and added enough money to cover the increases and to permit a modest increase in the number of grants. NCI was glad enough to get the extra money, and the grantees were happy to be fully funded, but some NCI executives, including Director Vincent DeVita, did not particularly like having the flexibility to stretch the paylines taken away from them.

The DCT Board, following a presentation on the current status of the budget by DCT Director Bruce Chabner, approved a motion calling on Congress to permit NCI to reduce funding levels in order to increase the payline. The vote was only 10-5, however, and Board Chairman Samuel Hellman and member M.M. Elkind expressed dissatisfaction with the lack of a stronger consensus. After further discussion, some members indicated they would rather take a somewhat more flexible position on the issue, but a new motion to modify the first by adding a request that Congress increase NCI's appropriations was tabled.

Board member Susan Horwitz opened the discussion by asking what the feedback had been from grantees who received less than full funding in previous years. "They were living with it but were complaining," Chabner said. "Considering our budget problems, they agreed to go along with it for the most part."

"I wonder what individual people would think about taking a four percent cut in RO1s in order to get the payline up to, say, 190 or 200," Board member David Goldman said.

Chabner noted that to raise the payline one point requires, roughly, an additional $1 million, and that cutting grants four percent would raise it about three points from the current level of about 175.

Board member Karen Fu expressed concern about lack of support for new investigators. Chabner responded that 20 percent of funded RO1s are new applicants, although "I don't know how many are in the category of young investigators."

"I disagree with making cuts from full funding across the board," Board member Brigid Leventhal said. "If you want more money spread around more grants, send that message to the study sections rather than to Congress."

"I feel strongly that most grantees can absorb a four percent cut," Horwitz argued. "With a cutoff of 175, if you get 176, you get zero funding."

"Congress left us a small amount of flexibility," Chabner said. "You could tell us to exercise all possible flexibility in extending the payline."

"I would hope that a statement from the Board would have the additional message that there is not enough money for research to begin with," Elkind said.

"We got an appreciable increase this year," Hellman said. "That message got across."

Goldman offered the motion, asking that "serious consideration be given to measures to increase the payline, one of which can be some kind of across the board cut from recommended levels."

Board member Carol Portlock asked that "there be some selectivity for young investigators, that we increase the payline for them if not for others."

Goldman agreed to add to his motion special consideration for young investigators.

"In considering grants, we don't consider age," Chabner said. "Just how good is the grant."

"I know some young people who are very good who are not going into academic medicine," Fu said. "There should be some consideration for people just starting their careers," Horwitz added.

"That is a dangerous course," Board member Dani Bolognesi said. "If you make a policy issue of raising the payline, you're mucking around with something very important. We could encourage the division to be flexible. I don't believe we can make a policy."

"I agree with Dani," Board member Efraim Racker said. "I think there are other modes of supporting young investigators."

Chabner pointed out that NIH does have a young investigator grant category, although the awards are not as large as RO1s. He also noted that "young people frequently get their start through program projects and center core grants. "I'm not saying the situation is great, but it is not as bad as it seems."

Chabner added that the congressional mandate included language calling for funding "at or near" recommended levels. "NIH has interpreted that to mean full funding unless there is some emergency."

Leventhal suggested that it is "probably illegal to pull out young investigator applications and fund them separately. The point has been made that there are different mechanisms."

"All of us agree with the sentiment of getting

more capable young people in," Board member Max Cooper said. "But I believe there are mechanisms for them and they are working. It is relatively easy to get that first grant. It's getting that first renewal that's tough."

Chabner suggested that the Board hear a presentation on existing mechanisms for supporting new and young investigators at its next meeting. Goldman agreed, "It's pointless to vote on this. We need more information."

Goldman went along with Elkind's suggestion that the first motion, which had already been approved, be brought back and amended to eliminate the language suggesting cuts from recommended levels to provide funds to extend the payline. The sense of the Board is that "there is clear dissatisfaction with the payline and the number of investigators being supported."

Racker moved to table the Elkind-Goldman motion, and it was approved. Hellman later made it clear that the Board was still on record with the first motion.

"But I intended (the motion to table) to apply to both," Racker said.

"It couldn't," Hellman insisted. "The first one had already been passed."

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs, citing the RFP number, to the individual named, the Blair building room number shown, National Cancer Institute, NIH, Bethesda, MD. 20205. Proposals may be hand delivered to the Blair building, 8300 Colesville Rd., Silver Spring, Md., but the U.S. Postal Service will not deliver there. RFP announcements from other agencies will include the complete mailing address at the end of each.

RFP NCI-CN-45186-41
Title: Biomedical computer support services
Deadline: Not available
This is a Small Business Set-Aside

NCI's Prevention and Control Contracts Section is soliciting requests for proposals from small business organizations interested in providing biomedical/biostatistical computer, research data management, and logistical support to the scientific programs of the Biometry Branch, the Operations Research Branch, and the Office of the Director of the Div. of Cancer Prevention & Control, NCI.

Services to be provided include: Computer program and systems development, documentation, and maintenance; utilization of available software from the NIH Div. of Computer Research & Technology in providing tabulations and graphs; operation of a clinical trials coordinating center; the development of technical reports including feasibility studies and system design specifications, medical coding, editing, data management, and logistical support.

A preproposal conference will be held within two weeks of the issue date and a "reading room" containing reference materials pertinent to this procurement will be made available.

Offerors must demonstrate the ability to be available witnin one hour's notice for meetings and for receipt and delivery of data, reports and documents to the Blair Building, 8300 Colesville Rd., Silver Spring, Md. 20910.

This procurement is a 100 percent set-aside for small businesses. For the purpose of this procurement a small business is classified as small if its average annual receipts for its preceding three fiscal years do not exceed $4 million.

Contract Specialist: Susan Hoffman
RCB, Blair Bldg. Rm. 2A07
301-427-8745

RFP Amendment

RFP NCI-CP-EBP-41010-65
Title: Operation of a computerized death certificate procurment and management system and tracing using other vital records systems

Date for receipt of proposals has been extended to Wednesday, April 3.

NCI CONTRACT AWARDS

TITLE: Preparation of bulk chemicals and drugs
CONTRACTORS: Aldrich Chemical Co., Milwaukee, Wis., $870,807; Aerojet Strategic Propulsion Co., Sacramento, Calif., $1,231,353; Pharm-Eco Laboratories, Simi Valley, Calif., $986,559; Warner Lambert, Ann Arbor, Mich., $1,079,916; Ash-Stevens, Detroit, Mich., $1,623,090; and Starks Associates, Buffalo, N.Y., $1,857,992.

TITLE: Office of Cancer Communications conference support project
CONTRACTOR: Birch & Davis Associates, Silver Spring, Md., $95,132.

TITLE: Support activities of the U.S.A. National Committee for the International Union Against Cancer (UICC)
CONTRACTOR: National Academy of Sciences, $140,000.

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