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DCT Board Approves Continuing Neutron Trials Past 1989 Expiration, With New Funding Plan

The problem plagued neutron therapy clinical trials supported by NCI since the mid-1970s will be continued at least through completion of the clinical trials already under

(Continued to page 2)

In Brief

Interim Dean Henney Looking For Cancer Center Director; Shingleton Gets James Ewing Award

JANE HENNEY, special assistant to the vice chancellor of the Univ. of Kansas Health Sciences Center, is in the process of recruiting a director for the university's fledgling cancer center. Haney, former NCI deputy director, is interim dean of the university's School of Medicine while a search goes on to fill that position. Candidates for the cancer center job may contact Henney at the center or the School of Medicine, Rainbow Blvd. at 39th, Kansas City, KS 66103. . . . **WILLIAM SHINGLETON**, director emeritus of the Duke Comprehensive Cancer Center, received the 1988 James Ewing Award from the Society of Surgical Oncology at the New Orleans meeting. His award lecture, "Cancer Centers: Origins and Purpose," discussed his experience as founding director of the center. Shingleton served two terms on the National Cancer Advisory Board. . . . **DAVID BALTIMORE**, director of the Whitehead Institute for Biomedical Research at Massachusetts Institute of Technology, has received the Memorial Sloan-Kettering Medal for Outstanding Support of Biomedical Research. Other awards presented at MSK's annual academic convocation were the Katherine Berkan Judd Award, for major advances in the control and cure of cancer, to Francis Ruddle, Yale professor of biology and human genetics; the Aaron Bendich Award, to an outstanding former student, to Robert Nowinski, president of Genetic Systems; and the C. Chester Stock Award for significant contributions to the advancement of knowledge on cancer, to Victor Ling, professor of medical biophysics at the Univ. of Toronto. . . . **RICHARD ADAMSON**, director of NCI's Div. of Cancer Etiology, has received the Dept. of Health & Human Services Management Award "for outstanding scientific and administrative leadership and contributions to affirmative actions and EEO goals". . . . **FULMER SHEALY**, head of the Medicinal Chemistry Div. at Southern Research Institute, is the first recipient of the institute's Scientific/Engineering Excellence Award for his work in developing anticancer and antiviral drugs.

BSC Recommends: Complete Neutron Trials, Base Payment On Accrual

(Continued from page 1)
way, the Board of Scientific Counselors of the Div. of Cancer Treatment decided Monday.

The Board accepted the recommendations of its Neutron Therapy Review Committee to extend the trials past the 1989 expiration date of the contracts still in force, probably for another five years.

The report of the committee, established following the Board's February meeting to develop recommendations on the program's fate, was accepted without debate or even any discussion. William Hendee, chairman of the committee and vice president for science and technology of the American Medical Assn., commented that "the lack of discussion is almost intimidating."

NCI has poured $65 million into neutron therapy grants and contracts since 1971, and Board members felt that that investment warrants spending a few more million to complete the clinical trials, some of which are very promising.

The committee's recommendations included a new funding mechanism, basing part of NCI's payments on accrual. Other modifications also were suggested.

Summary of the report and its recommendations:

The neutron therapy clinical trials program should be recognized as a major undertaking in scientific research, with the effort just beginning to show success in improved local control of advanced cancers and reduced complication rates in normal tissues. In a sense, the current program is a phase 2 clinical investigation; should the results continue to prove successful, they will justify the application of neutrons to early cancers in selected regions where the radiosensitivity to neutrons is most promising, or where the response to conventional therapies is most unrewarding. These trials will provide the final evidence concerning the curative potential of fast neutrons for cancer therapy.

The Neutron Therapy Review Committee recommends unanimously that the clinical trials program of fast neutron therapy be supported beyond 1989 to completion of the clinical studies. However, certain modifications in the current clinical trials are recommended:

<>The clinical trials for cancers of the head and neck and of the prostate are recognized as promising the most significant results. The importance of rapid accrual of patients into these trials is emphasized.

<>The accrual of patients into clinical trials for lung cancer and for resistant histologies is encouraged, but these trials are recognized as less significant than those for head and neck and for prostate cancer.

<>Contracts for the three institutions funded for the clinical trials program should be negotiated so that payment is based, in large measure, on patient accrual. The lump sum base support should be less than 50 percent of the total anticipated contract payment for the first year, and should be reduced in succeeding years to a payment of $0 after the third year.

<>Reimbursement from third party carriers should be sought for patients in neutron therapy trials, and two thirds of this reimbursement should be subtracted from the payment from NCI for the same patients.

<>Publication of the results of the phase 2 dose searching strategies is encouraged at the earliest opportunity.

<>Data from new institutions should not be added to the current data from participating facilities for purposes of the current trials.

<>Participating institutions should be encouraged to admit suitable patients into the clinical trials program at the fastest possible rate.

The report described early studies with neutron therapy, its mechanism and rationale for its use. The program in question began in 1979, when NCI funded construction of three hospital based state of the art neutron generators to allow researchers to study neutron radiotherapy with appropriate beam delivery support systems in a hospital setting.

Three 10 year contracts were awarded in 1979 to the Univ. of Washington, UCLA, and Fox Chase Cancer Center/Univ. of Pennsylvania. A fourth neutron generator was to be developed at M.D. Anderson Hospital, through a grant awarded the previous year.

Three of the four were to use cyclotrons, while Fox Chase was to adapt the deuteron on tritium reaction to produce a different kind of neutron generator.

The Univ. of Washington cyclotron was developed by the Scandanavian Scanditronix Corp. using 50 MeV positive ions on beryllium. The UCLA cyclotron contract was awarded to the Cyclotron Corp. of Berkeley, CA, which would deliver a neutron beam from 48 MeV negative ions on beryllium. Cyclotron Corp. would also build the MDAH cyclontron, using

42 MeV negative ions. Each facility was required to have two treatment rooms, one capable of isocentric beam delivery with a rotating gantry allowing treatment from any arbitrary angle or orientation, and the other treatment room to be equipped with a fixed horizontal treatment beam.

The contracts specified three phases of work: (1) equipment development and installation; (2) facility development and construction; (3) clinical trials. Phases 1 and 2 were to be accomplished concomitantly, and were projected to be completed by 1982, leaving at least seven years of the committed 10 year period for clinical trials.

However, equipment development proved to be more difficult than originally envisioned. While cyclotron technology was well developed in 1979, many problems remained to be solved in the delivery of a neutron beam through an isocentric gantry that could be oriented at any angle. Scanditronix successfully solved the problems in a reasonably timely manner for the Univ. of Washington. The other contractors, however, were not so fortunate.

Following a steady slippage of deadlines, Cyclotron Corp. filed for bankruptcy in 1983 and in January 1984 terminated operation. The machines for UCLA, MDAH and Fox Chase all suffered as a result. Each of the contractors was forced to carry out the tasks of final design, fabrication, assembly and testing. Costs mounted and deadlines slipped as the contractors coped with problems such as design deficiencies in the Cyclotron machines, incomplete drawings, nonmanufactured parts and unassembled electronics boards.

The Washington facility was completed first and made available for clinical testing in 1984. The Fox Chase D-T facility was also completed in 1984, but was plagued by chronic failures of the D-T tube and was ultimately scrapped in 1986 because of technical difficulties and high maintenance costs related to the high frequency of tube replacement.

The MDAH cyclotron was certified for isocentric treatment in July 1985. The UCLA facility treated its first patient in July 1986. Cleveland Clinic Foundation joined the Neutron Therapy Collaborative Working Group in October 1985, to conduct neutron therapy clinical trials using the NASA cyclotron. Both the Cleveland Clinic and MDAH grants subsequently were converted to contracts with cost sharing as an integral component. Fermi Laboratory also submitted a proposal to join the NTCWG as a contractor, but was rejected because of inadequate past performance in patient accrual.

Because of the equipment problems, clinical trials, which had originally been planned for a seven year period, were now reduced to a residual of 3.25 to 5 years, depending on the specific facility. In addition, the new neutron generators represented a departure from the earlier physics based machines, and the NTCWG decided wisely that the phase 1/2 dose searching toxicity studies were desirable before beginning phase 3 clinical trials. Randomized dose searching studies were initiated to determine the maximum tolerated neutron doses in the head and neck, thorax, abdomen, pelvis and extremities. These studies were completed in April 1987 with a total of 484 randomized patients.

Phase 2/Phase 3 Trials

Results of the phase 1/2 dose searching studies showed that the appropriate neutron dose for all phase 3 treatment sites would be 20.4 Gy in 12 fractions over four weeks, provided that field reduction is accomplished after 13.6 Gy in the abdomen and pelvis. Phase 3 trials were then designed to compare fast neutron radiation therapy against the best conventional treatment for squamous cell carcinomas of the head and neck, nonsmall cell lung cancers, prostate cancers, rectal cancers, cancers of the cervix and tumors of radioresistant histotypes including sarcomas and melanomas.

Patient accrual to the neutron studies currently totals approximately 850 in randomized studies, with a significant number of additional patients entered as "off study neutron subjects" on the phase 2 registry. These accruals translate roughly into 88 patients per facility per year, a rate that compares favorably with other oncology groups conducting clinical trials. Expected closure dates for the clinical trials are: head and neck, October 1994; prostate, June 1992; resistant histologies, September 1991; and lung, December 1989.

Neutrons show promise of providing an advantage over all other conventional treatments for prostate cancer. The prostate study will not be completed until approximately 1992. Radio resistant histotypes include the treatment of soft tissue sarcoma, osteosarcoma, chondrosarcoma, melanoma and renal cell carcinoma. Because of lack of patient accrual, phase 3 protocols in rectum and cervix were closed by the NTCWG at the most recent working group meeting in March of this year.

The lung protocol will be be completed before 1989.

Current neutron clinical studies do not utilize patients optimally suited for treatment. If the type of cancer most amenable to neutron therapy were known, either by site, histology or some other intrinsic characteristic, data about the value of neutrons could be gathered more quickly because the clinical studies could be focused more appropriately. Because this information is not known, more general clinical studies of the type supported by NCI are required to assess the possible benefits of neutron therapy.

Current phase 3 studies are confined to advanced tumors of the head and neck, and stage C-D carcinomas of the prostate, with a therapeutic result that may be compromised by the presence of concomitant or subsequent disseminated metastases. Selection of these tumors is understandable because surgery and megavoltage x-ray therapy, with or without chemotherapy and hormonal therapy, are often unrewarding, and neutrons have the potential to enhance local control. Realization of this potential will enhance the endorsement of neutrons for local control of cancer, even through in these particular clinical trial patients, survival may not improve dramatically because of the presence of metastases. Once the advantage of neutrons for improved local control of advanced cancer is established, however, the true curative potential for early cancers can be explored.

Of the current clinical trials for neutrons, potentially the most significant are those directed to cancer of the head and neck and prostate. The former yields definitive criteria of success or failure, and the latter is a relatively slowly growing tumor that, like salivary gland malignancies, may respond selectively to neutrons. The lung study is compromised by inclusion of chemotherapy at the Univ. of Washington; hence there are essentially two lung studies, and definitive conclusions may be difficult to develop with the number of patients scheduled for treatment. In the study of resistant histologies, soft tissue sarcomas and osteosarcomas are of primary interest; radiation therapy of the remaining sites may have less relevance to their management.

As of May 1, 1988, two facilities, Univ. of Washington and UCLA, are actively accruing patients to phase 3 trials. Although the Univ. of Washington has solicited more patients into clinical trials than has UCLA, currently both institutions are accruing patients at about the same rate. At the September 1987 review of these contracts by the Radiation Research Program, it was determined to terminate the Cleveland contract because of inadequate patient accrual. In October 1987, the MDAH facility suffered a major breakdown of the cyclotron, which is now being repaired at no cost to NCI. The facility is expected to return to normal operation in October 1988, following installation of a new magnet for the cyclotron.

UCLA and the Univ. of Washington are the only contractors currently receiving NCI support and they are funded through June 1988. No new funding is anticipated for the Cleveland Clinic for neutron therapy studies, although the unexpended balance of the original contract will be used to continue followup of data management studies of all patients treated with neutrons. MDAH will not receive new funds until the neutron beam is once more operational.

Both MDAH and UCLA contributed to the costs of their facilities from institutional funds. Excluding these costs, patient treatment costs typically have run $1 to $1.4 million per year with a fully operational facility. Washington was able to decrease its annual budget by 50 percent in 1987 through a recharge mechanism, whereby reimbursements for patient treatments from third party carriers are used to defray the operational costs of the cyclotron and neutron therapy expenses. Both MDAH and UCLA have also implemented mechanisms for capturing third party payment for neutron therapy treatments. Reimbursements through this mechanism have not yielded significant savings to NCI, however, because of the patient populations and geographical areas served by the two institutions. Approximately half the phase 3 patients at UCLA, for example, are VA patients for which third party reimbursement is unavailable.

International Neutron Therapy

There is a growing international interest in the U.S. neutron therapy studies, particularly those in the head and neck and the prostate. Certain facilities with neutron generators comparable to U.S. facilities have expressed a desire to participate in the U.S. studies without financial support from NCI, except for data management by the Radiation Therapy Oncology Group. Facilities include Clatterbridge group in Liverpool and investigators in Belgium, France, South Africa and Korea.

There are a total of four neutron facilities under various stages of development in France. Hammersmith Hospital in London is currently installing a new neutron therapy facility, as is Harper-Grace Hospital in Detroit. Fermi Laboratory continues to treat patients with neutrons paid for through third party reimbursement.

The Neutron Therapy Review Committee is encouraged by the international interest in neutron therapy and in the NCI supported clinical trials for this modality of treatment. However, it recommends against incorporation of patient data from new facilities for neutron therapy, irrespective of their location nationally or internationally. Quality control of the facilities and resultant patient data would be difficult to ensure, and addition of data from new facilities would compromise the existing bank of clinical data. Furthermore, NCI has invested a considerable sum in clinical trials at the three institutions remaining in the program, and they should recognize their obligation to accrue sufficient patients to complete each of the protocols without additional patients from other institutions. The U.S. experiment is the only controlled phase 2/3 clinical trial in existence for dedicated neutron therapy facilities, and it is finally progressing towards completion in a reasonably steady manner. It would be unfortunate if the integrity of this trial were compromised by the admixture of varieties of data in an effort to expedite completion.

James Cox and William Hryniuk were the other BSC members on the committee in addition to Hendee. Svi Fuks of Memorial Sloan-Kettering Cancer Center, Stuart Grossman of Johns Hopkins and Paul Todd of the National Bureau of Standards were also members.

BSC Gets Overview of Drug Groups, Clearing RFA For Natural Products

Another major program was given a green light to proceed as planned by the Div. of Cancer Treatment Board of Scientific Counselors this week.

The Board heard presentations by the four original National Cooperative Drug Discovery Groups and agreed that the program is fulfilling expectations in bringing multi-institution, multidisciplinary, academic, industry and NCI talent together to find new ways to develop new anticancer agents.

The first overview of the program since it was initiated four years ago had been scheduled prior to the Board's meeting last February, when it was asked to give concept approval for a new RFA to support new groups for development of natural product anticancer drugs. The Board approved the concept but made it conditional on how review of the first groups went.

It went well, with members expressing enthusiasm for the program. The motion to proceed was approved unanimously.

Michael Boyd, director of the Developmental Therapeutics Program, said the RFA for the natural products groups probably will be issued next month.

Presentations were made by Carl Porter, Roswell Park Memorial Institute, and Raymond Bergeron, Univ. of Florida, for the group on inhibitors of polyamine biosynthesis and function; by Warren Ross and Randall Johnson for the group on topoisomerases as chemotherapeutic targets; by Victor Levin, Univ. of Texas M.D. Anderson Cancer Center, for the group on inhibition of oncogene and growth factor related tyrosine kinases; and by John Mendelsohn, Memorial Sloan-Kettering Cancer Center, and Ian Trowbridge, Salk Institute, for the group on antireceptor monoclonal antibodies.

The groups reported varying degrees of progress, with productive collaborations and some agents in preclinical development stages and others nearing phase 1 studies. Mendelsohn has one now in phase 1.

"The (NCI) staff is very enthusiastic about this approach," Boyd said after the presentations. "Intent of the program is to enhance the likelihood of discovering new therapeutic entities. . . In these presentations today we heard a lot of biology, and we're hearing about screening and synthesis in ways we haven't heard before."

"This is a very exciting approach," Board member Robert Schimke said. "Essentially, it brings people together."

"This is one of the most interesting areas of drug development," Board member John Kersey said.

Susan Horwitz, who is serving a second term on the Board, commented that it was during her first term that the concept of national collaborative drug development groups was suggested by Alan Sartorelli, then also a member of the Board. "He was the key person, who worked the hardest, to set this up," Horwitz said.

Curt, Ozols, Browne Leaving NCI In Major Staff Changes At DCT

Jane Henney had to give up her position as NCI deputy director when her husband, Robert Graham, decided to leave his job as head of the Health Research & Services Administration to become executive director of the American Academy of Family Physicians, in Kansas City.

Maryann Roper, the current deputy director of NCI, will probably leave the Washington DC area when her husband, James Roper, is asked by whoever becomes HHS secretary next January, to give up his job as head of the Health Care Finance Administration.

There undoubtedly are other women scientists and science administrators who have had to adjust their careers to accomodate those of their spouses. It is only right, that for once, the shoe is on the other foot.

Suzanne Curt, an attorney with the Dept. of Justice, decided to accept a position in the U.S. Attorney's Office in Providence, RI. And that is why Gregory Curt, the popular deputy director of the Div. of Cancer Treatment, is looking for a job in that area.

In addition to being important to Suzanne Curt's career, the move returns the couple to their home area; both have family members there.

Gregory Curt is a medical oncologist, continued to see patients while holding down the DCT deputy job, and is considering several possibilities in the Providence area. He will leave NCI in July.

DCT Director Bruce Chabner said the deputy position will be competed, and asked that candidates or those with recommendations contact him.

Curt's departure is one of many staff changes Chabner announced this week, including another major loss from the Medicine Branch. Robert Ozols, head of the Developmental Therapeutics Section of the Branch, will leave in October to head medical oncology at Fox Chase Cancer Center.

Marcia Browne, who has been Chabner's special assistant for clinical affairs, will leave in August to become director of clinical research at the Roger Williams Cancer Center at Brown Univ.

William New, who has been administrative officer of the Developmental Therapeutics Program for seven years, will leave next month to become director of administration at New England Deaconess Hospital in Boston.

Dorothy Tisevich, DCT deputy administrative officer, has moved to the HHS Budget Office as its NIH analyst.

Chris Leinneweber, administrative officer for the Cancer Therapy Evaluation Program, has moved over to the National Institute of Allergy & Infectious Diseases as program analyst for AIDS.

Mace Rothenberg and Wyndham Wilson, both medical staff fellows in the Clinical Oncology Program, will move into Chabner's office as special assistants.

Kathy Russell, administrative officer of the Clinical Oncology Program, has become acting deputy administrative officer of the division.

John Bader, retrovirologist in the Div. of Cancer Etiology, has been named special assistant to Michael Boyd, director of the Developmental Therapeutics Program. He will be responsible for screening for anti-HIV compounds.

Richard Donovic, a pharmacologist with Squibb and later head of the American Type Culture Collection, has joined the DTP extramural staff as a cancer expert to aid in the development of the cell line screen for anticancer drugs.

Chabner announced at the meeting of the DCT Board of Scientific Counselors this week that the Medicine Branch and the Clinical Pharmacology Branch are being consolidated. Charles (Snuffy) Myers, chief of the Clinical Pharmacology Branch, had previously been announced as the new chief of the Medicine Branch, succeeding Robert Young, who is now director of the Centers & Community Oncology Program in the Div. of Cancer Prevention & Control.

"The new Medicine Branch will have responsibility not only for medical oncology at the Clinical Center, but also for the phase 1 and phase 2 trials of new AIDS drugs forthcoming from Sam Broder's laboratory," Chabner said.

Chabner also listed some of the staff members who will accompany Marc Lippman when he leaves next month to become director of the Lombardi Cancer Center at Georgetown Univ. They are Edward Gelman, Neal Rosen and Sandy Swain, all member's of Lippman's Medical Breast Cancer Section in the Medicine Branch; and Ed Sauseville of the Navy Medical Oncology Branch.

Chabner also revealed that Ken Cowan had been named to replace Lippman as head of the Medical Breast Cancer Section.

Younger members of the Medicine Branch staff moving up include Carmen Allegra, who

will head the new Colon Cancer Section; and Dwight Kaufman, formerly a research fellow at NCI who will return after two years at Roswell Park, who will work in the Radiation Oncology and Medicine Branches.

BSC Approves Two RFAs, Changes One To PA, Disapproves Another

The Div. of Cancer Treatment Board of Scientific Counselors gave concept approval for RFAs for two new grant supported projects, for studies of chronobiological effects in cancer treatment and for radiolabeled immunoconjugate dosimetry.

The Board changed another RFA proposal, for grants to support specific cancer cell targeting using molecular genetic technology, to a program announcement. That action dropped the $1 million recommended set aside for first year funding, and means that resulting applications will be reviewed by regular study sections rather than a special ad hoc review committee.

The Board disapproved entirely an RFA for improvements in the use of liposomes as delivery systems in cancer therapy. That proposal had $500,000 in set aside first year funds.

The concept statements and Board discussion:

Radiolabeled immunoconjugate dosimetry. Three year grants, estimated total cost for the first year, $800,000.

Radiolabeled immunoconjugates are being developed for diagnosis and therapy; some are in limited clinical testing. The results of these studies are promising and it appears that new antibodies and stronger binding methods for the radiolabel will be developed. While calculating the dose delivered by the low activity used in diagnosis is desirable, calculation of the dose delivered is mandatory in therapy when large quantities must be delivered to the neoplastic tissue for the desired improvement in patient survival.

Recent measurement by microdosimeters and observations from autoradiography have shown the distribution in tumors to be much more nonhomogeneous than could be appreciated by available nuclear medicine imaging, including SPECT. Dosimetry to date has not accounted well for this aspect or for irregularly shaped tumors. The use of an extended MIRD type calculation has been proposed, but MIRD's major assumption is homogeneous distribution of radionuclide. Present methods provide an estimate of dose, but clearly some modification of "normal" methods or new developments must be made. The dosimetry may even have to be modified for each antibody, radionuclide (alpha, beta or gamma emitter) and/or target. Thorough evaluation of cancer therapy using radiolabeled immunoconjugates requires the best calculation of dose that can be performed. About $220,000 a year is being spent presently to fund parts of four grants in this area.

Grants resulting from this RFA will fund multiple institutions to develop and validate radiolabeled immunoconjugate therapy dosimetry along diverse or similar research directions.

Specific cancer cell targeting using molecular genetic technology. Five year grants, estimated total first year cost, $500,000. That amount will not be set aside, with the Board's decision to change this to a program announcement. Grant applications in response to this announcement will compete in the RO1 pool.

Targeting of cytotoxic agents to specific tumor cells and not to normal cell populations is one of the major goals in the field of cancer treatment. Immunotoxin (a specific antibody covalently coupled to toxin) therapy has the theoretical capability of restricting cell killing to a defined antigen bearing cell population. However, several potential problems have been identified which may limit the use of this approach.

These problems include the rapid emergence of nonantigenic variants within a tumor, the shedding of some antigens from the tumor cell surface, and the development of a human anti-immunoglobulin response. Recent advances in molecular genetic technology now allow the consideration of new approaches to cancer treatment. One such approach is the regulation by specific promoters and enhancers of inserted genes resulting in the selective expression of cytotoxic molecules in tumor cells. This method would cause tumor killing or modification of tumor function from within the cell. Another strategy is the use of gene splicing techniques to construct hybrid molecules which consist of segments of toxins and cell surface receptor ligands. These molecules would target tumor cells at the level of the plasma membrane.

Results of recent in vitro experiments have shown that selective activation of tissue or tumor specific genes is realistic. Molecules can be constructed using molecular manipulations that contain specificity as well as induce toxicity. However, successful use of these techniques for cancer treatment will depend upon the efficient delivery of the genes or toxic molecules to the tumor in vivo, the expression of the genes within the cells of the tumor, and the limitation of gene expression in irrelevant tissues.

This PA will support novel approaches to specific cancer cell targeting using recombinant DNA technology. Construction of appropriate molecules or genes which would specifically alter the function of tumor cells is encouraged. Proposed studies could include the isolation of cell specific genes with unique promoter and enhancer regions. These molecules or genes should then be tested for efficacy in vivo in tumor bearing animal models addressing questions of delivery and specificity. Development of theoretical models which predict the functionality of the constructs would be considered relevant.

Board members Emil Frei and Robert Schimke commented that the proposal was too broad. "It's hard to get hold of," Frei said. "This is extremely diffuse, it overlaps gene therapy, immunotoxin. A lot of this is happening in the RO1 system."

"No they're not, that's the problem," Board Chairman John Niederhuber argued.

DCT Director Bruce Chabner suggested it could be a program announcement but pointed out that if it were left as an RFA, it would be easier to fund exceptions (grants over the payline) if that is found desirable.

"When therapy is the goal of a grant, it does not get the same support from a regular study section," Dan Longo, director of the Biological Response Modifiers Program, commented.

"That's not true, if it is good science," Board member Susan Horwitz said. She argued for reliance on the regular NIH review process.

"You're objecting because this would be reviewed by people interested in the field," Longo said, prompting a chorus of denials from the Board.

"You want review by people who agree with you," Schimke shot back, prompting more denials, from staff

members. "We shouldn't tamper with peer review."

The motion to approve it as a program announcement was passed unanimously.

Studies of chronobiological effects in cancer treatment with biological response modifiers and/or drugs. Five year grants, estimated total first year cost, $500,000.

Chronobiology is the study of the temporal relationships in biological phenomena. Preclinical and clinical chronobiological studies in the field of cancer treatment have led to observations of significant effects on tumor response, pharmacokinetics and toxicity of therapeutic agents when the circadian schedules of treatment were varied. In addition, immune cells including bone marrow precursor cells of experimental animals and man demonstrate circadian variations in number and subtypes of lymphocytes released into the circulation and the response of these lymphocytes to mitogenic stimulation. Although in many cases the mechanism of circadian dependence is not known, chronobiological considerations may be important in the design of cancer therapy protocols.

Investigations which seek to examine circadian effects on the efficacy of cancer therapy must take into consideration other factors influencing the variability of the subject population and the biological and immunological assays. This RFA would encourage studies designed to provide a rigorous experimental basis for chronobiological effects in cancer therapy using biological response modifiers and/or drugs.

Proposals in response to this RFA should focus on in vitro and in vivo preclinical studies of chronobiological effects on tumor therapy using biological response modifiers and/or drugs. The chronobiological influences on host effector functions, toxicity, pharmacokinetics and antitumor response should be addressed employing well defined and well controlled immunological and biological assays in established and appropriate animal tumor models.

"I don't understand the reluctance of people to acknowledge the large body of evidence supporting this," Board member William Hryniuk said.

"There is no question that chronobiology exists," Frei said. "But the difference was never greaat cytokinetically to translate into significant effects."

Stephen Creekmore, BRMP, said that different results were seen at various sites and with various drugs. "When they looked at adriamycin and platinum, there were major differences in animal and pilot studies."

"The differences in ovarian cancer were very large, Robert Wittes, director of the Cancer Therapy Evaluation Program, said. "The problem was that the trials were not well controlled."

"I like this," Schimke said. "My concern is that $500,000 may not be enough.

The motion to approve was passed, with only Lawrence Einhorn opposed.

Improvements in the use of liposomes as delivery systems in cancer therapy. Five year grants, estimated total first year cost, $500,000.

Board members disapproved this concept for much the same reason they objected to the proposal they changed to a program announcement. They felt that it should go to regular study sections. Frei suggested that it would be an appropriate mission for a collaborative drug discovery group, which would include academia and industry.

Board member Charles Balch disagreed, insisting the field needed stimulating, and suggesting that applications involving clinical trials "struggle in the RO1 pool."

Balch cast the only vote against disapproval.

RFAs Available

Requests for proposals 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 20892. 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-CM-97574-29
Title: Preclinical toxicology and pharmacology of drugs developed for AIDS and related illnesses
Deadline: Aug. 9

The Developmental Therapeutics Program of NCI's Div. of Cancer Treatment is seeking organizations to carry out pharmacology and toxicology studies, the data from which must be suitable for filing with FDA as part of investigational new drug applications.

The organizations should have the facilities and staff to carry out such studies and the management expertise to analyze and evaluate the data. As a minimum requirement, the contractors must perform all toxicology studies in accord with FDA's current good laboratory practice regulations.

Multiple contracts will be awarded and each will be administered on a task managed basis. Task orders will be issued under the funded cost reimbursement level of effort contracts resulting from this solicitation. Assignments are estimated to involve four to six chemical agents annually. The objectives of the task orders to be issued are:

--Validation of analytical methodology to quantitate drug plasma levels in laboratory animals and to measure levels in rodents and dogs treated with the agent under study.

--Determination of bioavailability of drug after parenteral and/or oral administration.

--Assessment of acute and subacute toxicity in rodents and dogs.

The principal investigator should have a doctoral degree in pharmacology/toxicology plus at least three years experience in directing, implementing and evaluating drug toxicity studies in experimental animals. The pathologist and analytical chemist should likewise have credentials which illustrate their competence and accomplishments in serving as critical team members in the conduct of such studies.

The government anticipates three awards on an incrementally funded basis. Each increment will be for one year and the total contract will be awarded for a three year period or or about April 30, 1989.

This is a recompetition of contracts currently held by Battelle Memorial Institute, Hazleton Laboratories America, and Midwest Research Institute.

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