THE CANCER LETTER

Vol. 10 No. 25
June 22, 1984

Subscription $150 year North America
$175 year elsewhere

P.O. Box 2370 Reston, Virginia 22090 Telephone 703-620-4646

DCT BOARD APPROVES LUNG CANCER DRUG DISCOVERY PROJECT, FIRST TARGETED ANTICANCER AGENT SEARCH

A new concept in drug development, targeted at finding anticancer agents aimed at a specific disease or site, will be initiated by the Developmental Therapeutics Program in NCI's Div. of Cancer Treatment following approval by the division's Board of

(Continued to page 2)

In Brief

REAGAN NAMES DAVID KORN NEW CHAIRMAN OF NCAB; CONSENSUS CONFERENCE ON LIMB SPARING PLANNED

DAVID KORN, appointed to the National Cancer Advisory Board last month, was designated chairman of the Board in a surprise announcement by the White House last Friday. He will replace Tim Lee Carter, who has been chairman for the past two years. Carter still has four years to go on his term. NCAB appointments are for six years, but the chairmanship is for a two year term. Carter is the first chairman since the NCAB was established by the National Cancer Act of 1971 not to be reappointed at least once. Korn is professor and chairman of the Dept. of Pathology at Stanford. He has served a term as chairman of the Board of Scientific Counselors of NCI's Div. of Cancer Biology & Diagnosis. Korn's appointment will satisfy the critics who felt that the chairman should be a scientist familiar with the Cancer Program. **NIH CONSENSUS** development conference on limb sparing treatment of adult soft tissue and osteogenic sarcomas has been scheduled for Dec. 3-5. The conference will focus on the clinical and histological evaluation of patients for prospective limb sparing treatment, methodology and end results of appropriate limb sparing treatment, and directions for future treatment strategies. . . . **RFA ON BASIC** research on factors that influence NMR relaxation times will be announced later this month. NCI hopes to fund four to eight grants with up to $750,000 earmarked for the first year of the program. . . . **NCI HAS** announced recruitment for the position of deputy director of the Div. of Cancer Treatment. The Senior Executive Service position pays from $58,938 to $66,000, with an additional $10,000 for physicians' comparability allowance. Copies of the announcement may be obtained from, or qualifications statement SF-171 and CV and bibliography submitted to Joyce Crooke, PMS, Bldg 31 Rm 3A08, NCI, Bethesda, Md. 20205, phone 301-496-6503. . . . **SOCIETY OF SURGICAL** Oncology has awarded lifetime memberships to William Hutchinson, founding director and president of the Fred Hutchinson Cancer Research Center; Armand Hammer, chairman of the President's Cancer Panel; and Hyen Kimm, of Shanghai.

TARGETED DRUG DEVELOPMENT MAY LEAD TO EFFORTS IN BREAST, COLORECTAL CA

(Continued from page 1)
Scientific Counselors of a new Lung Cancer Drug Discovery Project at an estimated annual cost of $655,000.

The project will be primarily an in house operation, located at Frederick Cancer Research Facility with DCT staff performing most of the work. Various support activities will be added to the existing contracts for the operation of FCRF.

While the project is aimed at developing agents to treat lung cancer, it has a broader objective. DTP Director Michael Boyd told the Board that it would "provide a unique opportunity to explore the value of a targeted strategy for drug development. With its initial focus on lung cancer, the immediate main goal would obviously be to find better drugs with clinical efficacy against the disease. As a secondary but nonetheless very important benefit, this project should allow an optimal analysis, and hopefully the resolution, of several critical but as yet uncertain issues concerning in vitro and in vivo cancer models and their relative utility or appropriate role in drug discovery and development. For example, foremost among these issues are those concerning the relative values of in vitro and in vivo screening models, the use of human vs. animal tumors, and the use of fresh tumor specimens vs. established cell lines."

Boyd said the project would bring to bear the best scientific talent available, state of the art technology and the total current knowledge of the particular disease categories in the development of new and better screening models. A "rather different orientation" than seen in the past will be used to identify compounds of interest, he said. Conventional criteria such as structural novelty and structural similarity to compounds with known activity will be supplemented to utilize current knowledge of unique characteristics of the major cancer type under study. "DCT presently has a critical mass of expertise and resources so that it can address the problem of lung cancer in light of the above perspectives and issues in a uniquely powerful way," Boyd said.

The resources brought to bear on the project should "collectively provide a national resource to stimulate and complement badly needed basic and applied research in this highest priority problem area," Boyd said. "At an appropriate point, DCT should actively publicize the availability of this resource to the scientific community as a means to stimulate wide interest in the investigation of new leads and hopefully the submission of a new spectrum of candidate compounds."

Boyd emphasized that "this project may be viewed as only a first step toward exploring the value of a more disease oriented strategy in anticancer drug development starting at the initial screening level. If any promise of real progress is forthcoming, and if sufficient resources are or can be made available, we should consider further expansion of this initiative along similar lines to include other major high priority tumor categories such as breast and colorectal cancer. We might also select other tumors for which we have some excellent potential human tumor models and expertise available, such as ovarian cancer and melanoma."

Reason for starting with lung cancer is that it remains one of the most common, most lethal, and least treatable diseases, Boyd said. Currently available drugs are essentially ineffective against most human lung cancers, and new drugs in the pipeline are probably not much better. Also, "we currently have within various areas of DCT a substantial number of senior staff and major research programs committed to a broad spectrum of basic and clinical research related to lung cancer."

The proposal almost was shelved when, after only a few perfunctory questions from Board members, it was rejected by a 5-2 vote, with most of the members not voting. It was saved by Board Chairman Samuel Hellman.

"I'm sorry, but I missed the reasons for opposing this," Hellman said.

"Because there is not much evidence that there are any drugs to test, and we already have three screening systems," Board member Brigid Leventhal answered.

"This is to screen for new agents because a lung cancer screening effort is not in existence," Hellman said. "This will establish a special screen for lung tumors. The biology exists for that."

DCT Director Bruce Chabner said that the program would not cost much additional money, since most of it would involve redirection of existing efforts. Also, "we know a lot about the biology of lung tumors, the metabolic characteristics. This has never been taken into consideration in drug design."

Board members Efraim Racker and Carol Portlock argued that Boyd's presentation did not include enough details. "How are you going to select the drugs? What is the biological rationale?" Racker asked.

"This should not be a fishing expedition. There should be a metabolic and physiological basis," Portlock added.

"It is not fair for us to make a decision on the basis of the information given us," Board member David Goldman said.

John Minna, chief of the NCI-Navy Medical Branch and one of the world's leading authorities on

lung cancer, described the panel of cell lines available for use in screening. "I don't know which drugs should be screened," he said. "A reasonable approach would be to screen for activity. I don't know which are the right assays to use."

"This is a Cadillac model of what has come before," Board member Dani Bolognesi said. "It will use the best of what we already have approved, in a focused way. It is exactly what we should be doing."

When Hellman asked the Board to reconsider the vote, it was approved unanimously.

Boyd will be the overall project coordinator. Robert Shoemaker, chief of the Cell Culture Section in the Drug Evaluation Branch, will coordinate the in vitro studies, both the cell line assays and the colony forming assays. Joe Mayo, chief of the Animal Genetics & Production Branch, will coordinate in vivo studies, with Adi Gazdar, chief of the Human Tumor Cell Biology Section in the NCI-Navy Branch, in charge of xenograft models and Mayo handling metastatic models. Daniel Ihde, chief of the Cellular Kinetics Section in the NCI-Navy Branch, will coordinate clinical liaisons.

The Board gave concept approval to the support of neutron therapy clinical trials through competitive awarding of contracts, at a cost estimated at $4 million a year.

Three of the existing facilities with clinically dedicated neutron generators are supported by contracts and three by grants. The new competition "will get everyone on the same mechanism, and get them together as a working group," Francis Mahoney, acting director of the Radiation Research Program, told the Board.

Karen Fu, chairman of the Board's Neutron Therapy Committee, presented the committee's report supporting the concept.

"To date, over 7,000 patients world wide, including 4,000 from the U.S., have been treated with neutrons or with mixed neutrons and photons," Fu said. "Although preliminary results suggest more favorable response in certain tumors such as the salivary gland tumors, soft tissue and bone sarcomas, metastatic cervical lymph nodes from head and neck primaries and malignant gliomas, no definitive conclusions can be made regarding the efficacy of fast neutron therapy at this time. This is due both to a lack of uniformity in treatment policies among the neutron therapy facilities and to a lack of controlled randomized trials.

"Part of the technical difficulty in conducting clinical neutron therapy trials has been the lack of hospital based neutron therapy machines. Most of the patients in the past have been treated at rather primitive facilities that were originally designed for physics research purposes. During the past decade, through funds provided by NCI, a number of hospital based neutron therapy facilities have been constructed or are near completion of construction. With the availability of these hospital based neutron therapy machines capable of delivering treatments using modern radiotherapy techniques, it would seem timely to carry out phase 3 clinical trials to establish definitively the efficacy of neutron therapy. Up to now neutron therapy projects had been very costly. Most of the funds were spent in the construction of the neutron therapy machines and treatment facilities. Now that most of the construction is completed or near completion it would not be as costly to continue these projects and to establish the efficacy of fast neutron therapy through cooperative phase 3 clinical trials. There is a consensus among the committee that an organized concerted effort towards this goal should be made at this time.

"Members of the committee are supportive of the concept of funding all neutron clinical trials through the contract mechanism. This would provide NCI an opportunity to have more participation in the design, review and approval of protocols and in determination of patient accrual requirements than is permissible under either grants or cooperative agreements."

The committee also recommended that:

1. In the design of neutron therapy protocols the quality and scientific standard of the protocol treatment should not be compromised by the technical limitations of some of the existing facilities.

2. The specific aims of the study should be more focused with priority given to disease sites in which local regional control by conventional radiotherapy is a major problem.

3. The minimum requirement of patient accrual should be 100 evaluable patients per year per institution.

4. A mechanism should be worked out whereby the amount of funding for an institution is adjustable according to the number of evaluable patients accrued per year after providing the basic maintenance cost.

5. A site visit should be included in the peer review process before funding these contracts.

6. It is anticipated that if all goes well it may be possible to accrue the number of patients required for the phase 3 studies by the projected contract completion date of 1989. However, provisions must be made to provide further funds required for the followup of those patients and the collection of data in the ensuing years.

Mahoney said that six contracts would be awarded "if all six (of the institutions with clinically

dedicated neutron facilities) survive peer review."

Serving on the committee were Board members Rodrique Mortel, Portlock and Fu, along with Chabner, Mahoney, Simon Kramer and Alfred Smith.

Leventhal, who objected to what she said was the high cost per patient of the clinical trial, cast the only vote against the concept. Hellman countered that "this is comparable to curative treatment with any other form of therapy. We're used to seeing only components of costs."

The Board approved two other Radiation Research Program concepts but tabled a third.

Evaluation of high energy electron beam treatment planning. Estimated annual cost, $600,000 for a three year contract to support four to five institutions in a working group for three years. This will be a competitive RFP. The staff description of the program:

Electron beams are useful in the treatment of some tumors using radiotherapy because of their unique dose localization relative to x-rays. The use of electron beams is increasing due to the availability of high energy linear accelerators. Also, the increased use of computers and new technologies such as CT, NMR, ultrasound and advanced contrast agents have greatly increased the sophistication of treatment planning. There has been no systematic study of the optimization of electron radiotherapy made possible by these new developments or the role of tissue compensation and error analysis in electron beam treatment planning.

This cooperative effort will provide a focused evaluation of the capability of improving electron beam dose distributions with presently available beam delivery systems, imaging systems and computerized treatment planning systems. Evaluation of the role of tissue inhomogeneity corrections, error analysis, advanced beam transport calculations and dynamic treatment will also be made.

Each contractor in the working group will calculate treatment plans for patients in treatment sites representing each major anatomical area. The specific sites and numbers of patients will be determined by the working group. Three dimensional calculations will be performed using tissue data derived from CT scans. Plans will be optimized for technique of delivery, electron energy and tissue compensation. Error analysis and evaluation schemes will be developed for the application of findings to the practice of radiotherapy.

This effort requires the participation of several institutions having a variety of treatment machines (electron beam energies) and calculational schemes. Large numbers of patients are required which necessitates the participation of more than one institution.

Neutron dosimetry materials studies. Three year noncompetitive interagency agreement with the National Bureau of Standards, at an estimated cost of $150,000 a year.

NBS has a facility for the calibration of dosimeters for measuring dose for photons but none for neutrons. Therefore, there is no national standard for neutron radiation therapy and no calibration laboratory for transferring that standard to practicing neutron therapy facilities.

A tissue equivalent ionization chamber will be designed, built and used for the national standard through this agreement. The calibration will be determined by using it as an absolute instrument (applying kerma, stopping power and W corrections); by comparison with a tissue equivalent calorimeter; by calculations; and by comparison with standards of other nations. After development of an appropriate standard NBS will then offer calibrations for neutron dosimeters used in the field.

The Board tabled a concept for a contract to conduct large animal model studies of radiation dose fractionation and volume effects on normal tissues. The four year contract would cost as much as $1 million a year according to staff estimates.

The concept was proposed because of the fact that significant differences in radiation response are known to occur with changes in dose fractionation and irradiated volume. "These factors have not been systematically studied and current models have failed to satisfactorily correlate with clinical observations," the staff description of the proposal said. "Better understanding of these effects will permit greater optimization of radiotherapy regimens. . .

"Normal tissues at risk for each major anatomical site will be identified and appropriate large animals chosen to model each tissue. Studies will be designed and carried out for the irradiation of the selected tissues for a variety of dose fractionation schedules and irradiated volumes. Scoring schemes will be developed and applied for appropriate late effect endpoints." and applied for appropriate late

"Large" animals would involve animals "bigger than a mouse," Mahoney said.

"This really is the tip of the iceberg," Mahoney told the Board. "If it goes well, we will probably come back to you for a lot more money."

That prospect, along with the $1 million a year price tag in the current estimate, was anything but encouraging to the Board. "This might be okay if you don't have anything else to do," Samuel Wells said. "This is after the fact research, and you still won't be able to see the late effects in humans. A million dollars a year is a lot of money."

Leventhal said that a different animal would be needed to assess the effect in each organ system. "You should be doing these studies in humans. I'm afraid we will spend a lot of money and not get information useful in the clinic."

"We know the larger the volume the lower the tolerance for late effects," Hellman said. "We don't know the quantitative relationship. . . But Brigid's point is absolutely correct. It's not my place to convince you of this, and I don't think I could justify it."

Hellman suggested that a scientific presentation be made to the Board at a future date on the late effects of radiation therapy in animals, and that the concept be deferred. The Board agreed.

The Board approved concepts for two new contract supported projects in the Biological Response Modifers Program and the recompetition of two others.

Preclinical assessment of monoclonal antibodies. Estimated first year award, $500,000, three years. Staff description of the project:

The ability to produce murine monoclonal antibodies against tumor antigens now exists in many laboratories. There is at present a tremendous amount of research and development in progress in industry, academics and government to determine the potential usefulness of monoclonal antibodies and immunoconjugates in tumor classification, tumor diagnosis, tumor detection and cancer treatment. Before a monoclonal antibody can be used in a clinical setting one must thoroughly establish the specificity of the antibody. This includes molecular characterization of the reactive antigen and determination of its cellular and tissue distribution. Screening of antibody against a variety of tissues to identify antigen positive tissues can greatly facilitate design of the best diagnostic and therapeutic modality. It would also be valuable to have information comparing new monoclonal antibodies with monoclonal antibodies in existence to define new specificities as well as cross reactive relationships among monoclonal antibodies for antigen recognition. Further, the development of monoclonal antibodies is dependent on preclinical information on general safety testing for adventitious agents such as viruses, testing for efficacy against various tumors in animal models, biodistribution and tumor localization specificity in vivo, and animal toxicology testing. Discussions over the last year held in the form of a retreat on specific track screening indicated a consensus that development of monoclonal antibodies for the clinic would be facilitated by a contract specifically designed to test and evaluate monoclonal antibodies.

The purpose of this contract would be to develop a centralized, coordinated program for uniform preclinical testing and evaluation of monoclonal antibodies and their immunoconjugates prior to entry into clinical trials. Such evaluation will be helpful and effective in defining, elucidating and predicting mechanisms of activity and clinical efficacy.

This contract would test and evaluate monoclonal antibodies and immunoconjugates in several test systems: (1) immunoreactivity against a panel of known tumor cells to define relationships with other monoclonal antibodies and establish epitope reactivities by molecular or serologic means; (2) in vitro cytotoxicity assays, soft agar cloning assays; (3) virus testing for LCM, retrovirus and the MAP test; (4) immunohistologic screening to define antigen positive tissues and specificity; (5) antitumor effects in the nude mouse model and subrenal capsule assay; (6) animal toxicology evaluation in rodents and perhaps primates. Monoclonal antibodies will be evaluated at each level of testing and must pass the requirements of specificity and sterility before proceeding to the next level of evaluation and to the clinic.

Hellman cut short the presentation by Ronald Herberman, BRMP acting director, "because I know the Board approves this wholeheartedly." Bolognesi added, in making the motion for approval "with boundless enthusiasm, this is exactly what this program should be doing." There were no dissenters.

Development of screening procedures for testing the potential antitumor efficacy of human lymphokines on human cells. Estimated annual cost, $150,000, five years.

Lymphokines are considered as the nonimmunoglobulin factors produced by mononuclear cells involved in initiating, expanding, regulating or expressing the immune response. These factors may be useful in attempts to modify cancer patients' responses to their tumors or may have direct effects on malignant cells. Lymphokines may be useful in increasing the expression of the tumor cell killing potential of cytotoxic T-lymphocytes, macrophages, and natural killer cells in patients, thereby generating therapeutic effect. Use of some lymphokines may help alleviate some of the immunosuppression seen in both treated and untreated cancer patients, giving the patient greater immunoreactivce potential against not only cancer cells but also against life threatening infections.

Objectives of the contract are to (1) develop and standardize methods of effectively screening human lymphokines for direct and indirect anticancer effectiveness in vitro utilizing human cells as effector cells and several different human tumor cells as targets; (2) for human lymphokines that are not species specific, to develop methods of testing the effectiveness of in vivo administration of human lymphokines in animal models to (a) modify the ability of cancer bearing host to react to its tumor and (b) effect restoration of depressed immune reactivity caused by chemotherapeutic or radiotherapeutic treatment procedures for by the tumor itself; (3) to evaluate human lymphokines supplied by the BRMP in the above mentioned screening procedures.

Lymphokines are intimately involved in the initiation, expression and regulation of the immune response and some lymphokines have direct effects on other cell types, including tumor cells. Numerous lymphokines are described in the scientific literature. Certain aspects of lymphokines' effects point toward their potential usefulness in attacking cancer cells either directly or indirectly but information regarding their potential for treating patients with diseases is sparse or nonexistent. The development of a screening mechanism for testing purified lymphokines for their potential therapeutic usefulness will greatly assist NCI in evaluating lymphokines as biological response modifiers in cancer bearing hosts. Certain lymphokines have already been shown to have antitumor effects in vitro (i.e. lymphotoxin) and in vivo (i.e. tumor necrosis factor). Others (i.e. IL-2) have been shown to be able to expand cell populations with tumor cell killing capabilities. Such systems can be further developed to screen other lymphokines for beneficial antitumor cell effects. New and novel systems also need to be developed to screen purified

lymphokines either alone or in combination with other lymphokines or with other treatment modalities. This would assist NCI in determining which of these factors have the greatest therapeutic potential and which factors should be further developed as biological response modifiers.

Initial emphasis of screening procedures will be to focus on detailed analysis of two or three lymphokines of high purity. Additional emphasis will be given to the development of positive and negative controls for relevant assays.

Chemical coupling of cytotoxic agents to tumor reactive monoclonal antibodies. Estimated annual cost, $375,000, three years. This is a recompetition of a contract now held by Hybritech Inc.

Hybridoma generated monoclonal antibodies directed against specific antigens expressed on human tumor cells offer enormous possibilities for selective target tissue destruction when coupled to cytotoxic agents since they react with a limited number of cell types and can be obtained at high titers. The use of monoclonal antibody-cytotoxin conjugates for selective tissue destruction is strengthened by several studies with heterologous antitumor antibodies indicating that antibody drug complexes can be obtained that retain antigenic specificity and cytotoxic reactivity. The possibility exists for developing conjugates with high specificity and affinity for target tumor antigen that can selectively deliver a cytotoxic agent to a tumor site in vivo and may produce tumoricidal effects by promoting cytotoxicity in excess of either antibody or cytotoxic agent alone.

Because of these considerations there is a need systematically to evaluate and compare the cytotoxic properties of specific monoclonal antibody preparations coupled with different cytotoxic agents by appropriate in vitro and in vivo tests. The purpose of this contract is to conjugate or chemically couple several cytotoxic agents to monoclonal antibodies directed against antigens found on human tumor cells. Immunoconjugates will be evaluated in animal model systems and subsequently used in phase 1 clinical trials.

Experiments have been ongoing to couple adriamycin, ricin A chain, indium-111, yttrium-90 and iodine-131 to three monoclonal antibodies: T101, an antibody directed against a human T-cell differentiation antigen; 9.2.27, an antibody directed against a human melanoma cell antigen; and D-3, an antibody directed against a tumor specific guinea pig antigen. The contractor has supplied radioisotopes conjugated to T101, 9.2.27 and D-3 for animal model studies and for biodistribution and imaging studies with T101 in humans. Preclinical in vitro and in vivo studies are currently being performed with T101-adriamycin, T101-ricin, D-3 adriamycin, 9.2.27 adriamycin and D-3 ricin. Research grade T101-vindesine and 9.2.27-vindesine have also been prepared and preclinical studies are underway. It is expected that by midsummer, T101-adriamycin will be available in quantities and quality for a clinical study. In performing these studies, the contractor has performed appropriate tests on conjugates to demonstrate that the cytotoxic agent-antibody conjugates retain antigen-antibody specificity comparable to unmodified antibody and cytotoxicity in excess of the nonderivatized cytotoxin. The contractor also has scaled up the appropriate conjugation procedures to provide sufficient quantities of a human use product for preclinical and clinical evaluation. Experiments have also been carried out on those conjugates for clinical trials involving biodistribution, pharmacology and required safety testing for IND submission.

This contract will continue to use the most efficient procedures currently available to couple chemotherapeutic drugs, toxins and radioisotopes to monoclonal antibodies directed against specific antigens found on human tumor cells. Several compounds are currently available for conjugation and include ricin A chain, abrin, gelonin, vindesine, pseudomonas toxin, bleomycin, cytoxan, methotrexate, adriamycin, indium-111, iodine 131, and yttrium-90. Several monoclonal antibody preparations are in various stages of development, and it is expected that antibodies specific for colon, lung, breast, and neuroblastoma will be ready for conjugation. When several methods are available for conjugation the contract shall determine the most efficient procedure. It is anticipated that some toxin-antibody conjugates may be formed by creating fusion products following cloning of individual antibody and toxin genes with hybrid expression using recombinant DNA technology. The contractor shall carry out purification of conjugates and show that the complex is stable. Tests must also be carried out to demonstrate that the conjugates retain antibody-antigen specificity comparable to unmodified antibody and cytotoxicity equivalent to nonderivatized cytotoxin. The contractor will be required to scale up the successful conjugation product to provide sufficient quantities of selected conjugates for preclinical and clinical evaluation. Procedures must be carried out under conditions to provide sterile, human use products.

"To what extent does the complex penetrate the vascular wall?" Goldman asked.

"It is clear that we can make conjugates with drugs like vindesine and adriamycin and that they do get into cells which have the antigen," Herberman said. "There is no question, that in vitro and in vivo, although we are still in the early stages, the results are fairly promising."

Production of hybridomas secreting antibodies reactive with human cytokines. Estimated annual cost, $175,000, three years. This is a recompetition of a contract presently held by Memorial Sloan-Kettering Cancer Center (Hellman, physician in chief of Memorial Hospital, left the room when this was brought up).

Several functionally and biochemically unique soluble proteins have been discovered that play a central role in regulating the responsiveness of the immune system and/or act as antigen nonspecific effector molecules capable of mediating one or more aspects of immune function. These factors may be synthesized by lymphoid cells, macrophages, tumor cells or other cell types. All of these factors are

included under the generic term cytokine. Representative examples include interleukin 1, interleukin 2, macrophage activating factor, tumor necrosis factor, interferon, lymphotoxin, products of suppressor T cells, products of helper T cells, etc. Other cytokines such as peptide growth factors, and products of oncogenes that biologically modify tumor cells are also included. Recent refinements in protein chemistry and separation techniques, the development of continuous lymphoid cell lines secreting particular cytokines, and the potential for cloning cytokine genes in microbial systems by recombinant DNA technology have made production and purification of many of the substances possible. Therapeutic effects may be anticipated either by the addition of those cytokines capable of activating an antitumor immune response or conversely by inhibition of cytokines responsible for suppressing an antitumor immune response or inhibition of peptide growth factor cytokines that biologically modify tumor cells.

Monoclonal antibodies reactive with specific human cytokines will provide powerful tools to investigate the usefulness of anticytokine therapy in human cancer. Monoclonal antibodies may also be useful in the purification of human cytokines and in determining the specific biological effects of cytokines in a variety of in vitro systems. For these reasons the BRMP seeks contractors with expertise necessary to produce hybridomas secreting monoclonal antibodies reactive with various human cytokines.

The present contractor has prepared five monoclonal antibodies (A7, B24, 114, L12, and M2) recognizing different epitopes of the human natural IFN-gamma. Antibodies were prepared by immunizing BALB/c mice with a highly purified human natural IFN-gamma preparation. All five antibodies had high IFN-gamma binding activity but exhibited differential IFN-gamma neutralizing activities. Furthermore, none of them neutralized the antiviral activity exhibited by both IFN-alpha and IFN-beta preparations indicating their specificity for IFN-gamma. Preincubation of the natural as well as E. coli derived IFN-gamma preparations with four, except B24, monoclonal anti-IFN-gamma antibodies indicated a neutralization effect on the augmentation of natural killer cytoxicity by IFN-gamma but not by IFN-alpha2 preparation. All five monoclonal antibodies precipitated an identical molecular complex containing two major protein component with molecular weights of 20,000 and 25,000 daltons and two minor components with molecular weights of 17,000 and 45,000 daltons. These monoclonal anti-IFN-gamma antibodies should prove useful as probes for plurification and for rapid assay of human IFN-gamma molecule.

The contractor also has prepared highly purified human IL-2 by ammonium sulfate purification, DEAE cellulose ion-exchange chromatography, ultragel filtration and chromatography over blue agarose and procion-red agarose columns. Two major protein bands of MW 16 and 17KD were visualized on SDS-PAGE by silver staining. BALB/c mice have been immunized with this material and fusion experiments performed. The contractor is now screening hybridoma clones for monoclonal antibody secretion with radiolabeled human recombinant IL-2. Following identification of positive clones small scale ascites production and antibody purification will be performed.

Human B-cell growth factor has been purified to apparent homogeneity and has a MW of 17KD by SDS-PAGE. The contractor has scaled up purification and initiated immunization of mice for monoclonal antibody production.

Mouse tumor necrosis factor (TNF) has been purified to homogeneity and immunization of rats for monoclonal antibody production initiated. Production of MoAb to human TNF is in collaboration with Lloyd Old.

This contract will continue to produce hybridomas secreting monoclonal antibodies against cytokines. Cytokines will be made available to the contractor when pure sources are available. In some instances the contractor will be responsible for isolation of cytokines of interest to the BRMP. In each case the contractor will develop the most efficient procedure to produce and isolate human or mouse MoAb against human cytokines. The contractor will be required to devise the most appropriate immunizing protocols and screening methods to confirm the immunogenicity of the human cytokine in mice and to assay hyridoma clones for antibody reactivity against individual cytokines. In most situations immunochemical rather than biological assays will be required to confirm the production of cytokine binding hybridoma derived antibody. In general radioimmune binding assays for the specified cytokines will need to be developed by the contractor for analysis. In each circumstance, the demonstration of the ability of monoclonal antibody specifically to inhibit a cytokine will be required. The contractor will be required to grow sufficient hybridoma cells to establish a frozen cell bank of at least 10 to the eighth cells in aliquots of 10 to the sixth cells. The aliquots must be sterile and on culturing thawed cells, viable antibody secreting cell lines must be obtainable. The contractor will provide frozen aliquots totaling 10 to the eighth hybridoma cells to the BRMP for use by the government.

The Board approved Herberman's request to double the amount previously approved as the maximum estimated for a contract to produce a liposome pharmaceutical for delivery of agents capable of activating macrophages. After the proposals came in, it was obvious the original $250,000 a year for the three year contract would not be sufficient, Herberman said.

Additional concept actions by the Board will be published next week in **The Cancer Letter.**

FIRST MOBILE NMR SCANNER BEGINS OPERATION AT TEMPLE UNIV. HOSPITAL

The world's first mobile nuclear magnetic resonance scanner began operation last week in a truck trailer parked in front of Temple Univ. Hospital. It will be shuttled between there and St.

Christopher's Hospital for Children, the pediatric division of Temple's medical school.

The machine, called the Beta 3000M by its manufacturer, the Fonar Corp. of Melville, N.Y., "has been producing superb images" in tests on patients in the past several weeks, according to Leon Malmud, chairman of the Dept. of Diagnostic Imaging at Temple.

The Fonar machine uses permanent magnets which do not require electricity for their activation and thus do not need extensive cooling systems. It does not have a "fringe field" outside the scan room, unlike the superconductive and resistive magnet NMRs which must be installed in heavily shielded rooms to protect against interference with electronic equipment.

The inevitable proliferation of demand for NMR use in diagnosis, particularly for suspected malignancies and in following the course of cancer treatment, has led to great concern about further increasing the cost of medical care. At the heart of that concern has been the expectation that every hospital will feel pressured to have its own NMR facility, with most of them being underutilized. There has been little if any consideration given to the possibility that a single NMR machine could serve several institutions, probably because few realized it would be possible to build mobile facilities. Mobile CT scanners have gone into service in recent years, making that technology available to institutions which may not have the number of patients to justify purchasing their own. But a mobile NMR seemed out of the question.

To everyone perhaps except Raymond Damadian, Fonar president and the first to see the possibilities for the medical application of NMR.

Damadian published the first scientific report on the theory of NMR in medicine for diagnosis and treatment followup in 1971 ("Science"). He obtained a patent in 1974, founded Fonar in 1978, and in 1980 produced the first commercial NMR scanner with a permanent magnet. Last month an FDA advisory panel recommended Fonar's machine for premarket approval.

Damadian told **The Cancer Letter** that his machine is comparable in price to those of his competitors, about $1.6 million for the stationary units. The mobile unit costs $2 million, including the scanner, truck and cost of installing it on the truck.

Damadian said that seven stationary Fonar machines are now in operation—at UCLA, Chicago Medical School, Brunswick Hospital in Amityville, N.Y., Montvale Diagnostic Imaging Center in Montvale, N.J., and one each in Japan, Milan, and Monterrey, Mexico. Seven more are on order, including orders from the Hospital Corp. of America for its flagship Parkview Hospital in Nashville, and diagnostic centers in Manhattan, Santa Monica, Beverly Hills, and Odessa, Texas.

Damadian claims the Beta 3000 is less expensive to operate and maintain than other NMRs. He said that compared to a supercon, the Beta 3000 can cost $500,000 less a year to operate. Based on 1,500 scans annually, a single Beta 3000 scan costs 42 percent less than a supercon scan.

Damadian said a scan by competing NMRs takes only two images, at two data points, requiring eight minutes per image. A Beta 3000 scan collects 13 images from 13 data points in one minute. He insists that the quality of the image produced by his machine is at least as good as those of his competitors, and in fact says they are superior.

An NCI executive involved in the Institute's NMR program agreed that the Fonar images he had seen in a demonstration were of good quality. Whether they will consistently compete in quality with those of the other machines remains to be seen, he said.

Damadian said the magnets in his machine "will last forever. We warrant them for 1,000 years."

Damadian appears to have gotten the jump on the rest of the industry, with a mobile machine available early in the development of NMR. The concept of mobile CT scanning was not developed until after hundreds, perhaps thousands, of institutions had already purchased their own equipment.

A few months ago, James Holland, chairman of the Dept. of Neoplastic Diseases at Mount Sinai Medical Center, suggested that NMRs be networked with the use of computer communications (**The Cancer Letter,** March 23). Utah radiologists David Bragg and James Nelson called Holland's suggestion "unrealistic and impractical" (**The Cancer Letter,** April 20).

Holland's plan envisioned centrally located NMRs to which patients would be transported, with their physicians viewing the results through their office computers. In a letter responding to Bragg and Nelson, Holland said, "It is clearly impractical for every community hospital to have one, and it is unrealistic to deny physicians in hospitals such as Mount Sinai, Einstein, Presbyterian, Bellevue, etc. in New York City the opportunity to employ NMR for their own needs."

The availability of mobile NMRs would appear to greatly enhance the practicality of Holland's theme, if not the precise details of his suggestion.

The Cancer Letter _Editor Jerry D. Boyd

Published forty-eight times a year by The Cancer Letter, Inc., P.O. Box 2370, Reston, Virginia 22090. Also publisher of The Clinical Cancer Letter.