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ALL 59 CCOP AWARDS ANNOUNCED: HEAVY IN NORTHEAST, FAIR IN MIDWEST; AMOUNTS, PRIORITY SCORES LISTED

The complete list of 59 Community Clinical Oncology Program awards was released this week by NCI, revealing a heavy concentration of CCOPs in the Northeast, fair distribution through the eastern Midwest states, and a scattering of others around the rest of the country.

NCI did not release dollar awards or priority scores, but those were

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In Brief

ELION, SCHEIN, JOHNSON HEAD SOCIETIES; PHILLIPS, SALMON ELECTED; McINTIRE, PISTENMA TO LEAVE NCI

NEW OFFICERS for the three societies which held their annual meetings in San Diego last month are: **Gertrude Elion**, Wellcome Research Laboratories, who became the third woman president in the 76 year history of the American Assn. for Cancer Research (the others were Thelma Dunn, 1961-62, and Charlotte Friend, 1975-76). Gerald Mueller is the retiring AACR president. **Frederick Phillips**, Memorial Sloan-Kettering and former secretary treasurer of the organization, was elected vice president and president elect. Robert Handschumacher was reelected secretary treasurer. **Philip Schein**, Georgetown Univ., took over as president of the American Society of Clinical Oncology, replacing Saul Rosenberg. **Sydney Salmon**, Univ. of Arizona, was named president elect. Two new directors are Charles Coltman and Stephen Rosenberg. David Ahmann was reelected secretary treasurer. **Judi Johnson** was elected new president of the Oncology Nursing Society, replacing Connie Henke Yarbro, who had served for the past four years. Johnson is with North Memorial Medical Center in Minneapolis. Delores Esparza, M.D. Anderson, remains as vice president; Barbara Medvec, Univ. of Michigan Hospital, was elected secretary; and Ruth McCorkle, Univ. of Washington, and JoAnn Wegmann, Long Beach (Calif.) Community Hospital, were elected as new directors. . . . **TWO MAJOR** vacancies will occur at NCI this year. Robert McIntire, chief of the Diagnosis Branch in the Div. of Cancer Biology & Diagnosis, will retire July 1 after 22 years with NCI. He will go into private practice in Falmouth, Mass. David Pistenma, who heads the Radiation Research program in the Div. of Cancer Treatment, will leave Oct. 1 to enter private practice in Fairfax, Va. . . . **GEORGE OMURA** has been elected chairman of the Southeastern Cancer Study Group, with his term extending through January, 1986. He replaces John Durant, who gave up the chairmanship when he became president of Fox Chase Cancer Center last year. . . . **JUNE MEETING** of the Cancer Clinical Investigation Review Committee was omitted from the meetings list in the May 27 issue of ***The Cancer Letter***. It will be held June 27-29, NIH Bldg. 31 Rm. 10, open June 27, 8:30-9 a.m.

NCI PLANNING MORE AWARDS, MAY ASK SOME TO TAKE CUTS FROM BUDGETS

(Continued from page 1)

obtained by ***The Cancer Letter*** from other sources and appear with each funded CCOP and most of the research base affiliations (see below).

The six exceptions which were funded beyond the payline cutoff of 247 did help achieve a somewhat better distribution of CCOPs in the less densely populated areas of the country. They are located in Spartanburg, S.C.; Charleston, W.Va.; Little Rock, Ark.; Fargo, N.D.; Las Vegas, Nev.; and Honolulu.

The total dollars required to fund the 59 CCOPs and their research bases, including indirect costs, will be a little less than $8 million, according to NCI's best estimate at the moment. This includes somewhat in excess of $5.3 million for the CCOPs and $2.5 million for the cooperative groups and centers serving as research bases.

If those figures hold firm, NCI will have about $2 million to fund additional CCOPs from those approved with priority scores in excess of 247. Based on the average cost per CCOP in the 59 awards of about $135,000, the additional $2 million would fund about 14 more. However, NCI staff is considering asking the CCOPs next in line to accept reductions from the recommended budget levels in order to permit funding of a greater number.

Total number of patients committed by the CCOPs to research protocols was 6,039. If that figure is maintained (there are those who feel it is conservative and will be between 7-8,000, especially if additional CCOPs are funded), that should be of major significance for clinical trials programs in the U.S.

The cooperative groups came away with most of the research base affiliations. The specialty groups accounted for 43 percent of the affiliations, general cooperative groups 33 percent, and regional groups six percent. Cancer centers were listed on 18 percent of the applications.

The median priority score was 258, with the range from 118 (the best) to over 400 (500 is the worst possible score). A large number of applications were disapproved outright for a variety of reasons, ranging from "too small" to "too big." One was rejected although it asked for zero dollars, another because the reviewers felt the applicant "is not really interested in doing clinical trials (why did he apply, then?). Still another, although approved, was marked down out of the present funding range because "they already have enough NCI support," thus penalizing excellence.

Considering the number of applications, the fact that this was a new program with not much precedence on which to base many decisions, and the relative inexperience of both applicants and reviewers in NIH grantsmanship, NCI staff members feel the review was fair. Some of the inequities which did arise may be corrected through the funding of additional awards, a process that probably will not pay much attention to priority scores.

Following are the 59 CCOPs which were approved for funding by the National Cancer Advisory Board. Included are the name of the CCOP organization, the administration headquarters if that differs from the CCOP organizational entity, the principal investigator, the priority score assigned by the NCI review committee, the direct cost awarded to the CCOP (not including the research base cost), the number of patients to be committed to research protocols, and the affiliated research bases. The order of listing is by priority score.

- Medical Center Cancer Protocol Program, Eastern Maine Medical Center, Bangor; Hadley Parrot; 118; $64,500; 99 patients; RTOG, Farber, CALGB, GITSG.
- Tri-State CCOP, Children's Hospital Research Foundation, Cincinnati; Albert Schreiner; 118; $60,820; 93 patients; SEG, NSABP.
- Geisinger Clinic and Medical Center, Danville, Pa.; Albert Bernath; 129; $67,666; 104 patients; MAOP, RTOG, CCSG.
- Bergen-Passaic CCOP, Hackensack Medical Center, Hackensack, N.J.; Allan Krutckik; 129; $84,245; 129 patients; ECOG, MSK.
- Southern Maine CCOP, Maine Medical Center, Portland; Ronald Carroll; 133; $63,800; 98 patients; CALGB, Farber.
- Columbus CCOP, Grant Hospital, Columbus, Ohio; Jerry Guy; 148; $85,656; 131 patients; SWOG, OSU.
- Twin Tiers CCOP, Our Lady of Lourdes Hospital, Binghamton, N.Y.; Robert Enck; 161; $75,429; 116 patients; ECOG, RTOG, GITSG.
- Allegheny CCOP, Allegheny Singer Research Corp., Pittsburgh, Pa.; Reginald Pugh; 162; $64,175; 98 patients; SWOG, RTOG, NSABP.
- Evanston Hospital, Evanston, Ill.; Janardan Khandekar; 162; $75,396; 85 patients.
- Southwest Washington CCOP, Consolidated Hospitals, Tacoma; Gale Katterhagen; 163; $75,898; 116 patients; SWOG, Hutchinson.
- West Metro-Minneapolis CCOP, St. Louis Park Medical Center, Minn.; Joseph Ryan; 170; $130,365; 200 patients, ECOG.
- Halifax Hospital Medical Center, Daytona Beach, Fla.; Herbert Kerman; 172; $39,377; 60 patients; ECOG, RTOG.
- CCOP of Roanoke, Roanoke Hospital Assn., Roanoke, Va.; Stephen Rosenoff; 179; $57,512; 88 patients; MAOP, Lombardi, POA, GOG, CALGB, NSABP.
- Duluth Clinic Ltd., Duluth, Minn.; James Krook; 181; $87,825; 135 patients; Mayo, NCCTG, ECOG, CCSG.
- North Shore Univ. Hospital, Manhasset, N.Y.; Vincent Vinciguerra; 183; $64,046; 98 patients.
- Hospital of St. Raphael CCOP, New Haven, Conn.; Leonard Farber; 184; $54,198; 83 patients; Yale, RTOG, ECOG.
- Kalamazoo CCOP, Borgess Medical Center, Kalamazoo, Mich.; Phillip Stott; 184; $59,913; 92 patients; ECOG.
- Greater Los Angeles CCOP, Hospital of the Good Samaritan, Los Angeles; Jim Bonorris; 185; $67,700; 104 patients; USC, SWOG.
- Florida Pediatric CCOP, Florida Assn. of Pediatric Tumor Programs, Gainesville; James Talbert; 185; $67,318; 103 patients; POG.
- Essex County Cancer Consortium, St. Barnabas Medical Center, Livingston, N.J.; Rodger Winn; 185; $66,690; 102 patients; MSK, GOG.

• Mary Imogene Bassett Hospital, Cooperstown, N.Y.; Richard Horner, 192; $48,510; 74 patients; ECOG, GITSG, NSABP.

• Methodist Medical Center of Illinois, Peoria; Stephen Cullinan; 194; $141,575; 217 patients; Mayo Clinic, NCCTG, RTOG.

• St. Joseph's Hospital Health Center, Syracuse, N.Y.; Kenneth Gale; 194; $104,337; 160 patients; ECOG, GOG, NSABP, GITSG, Roswell Park.

• Toledo CCOP, Flower Hospital, Sylvania, Ohio; Charles Cobau; 195; $96,125; 147 patients; ECOG.

• Marshfield Medical Foundation, Marshfield, Wisc.; Tarit Banerjee; 197; $68,234; 104 patients; ECOG, RTOG, NSABP, CCSG, U. Wisconsin.

• Nassau Hospital, Mineola, N.Y.; Larry Nathanson; 197; $54,050; 83 patients; CALGB, GITSG.

• St. Francis Regional Medical Center, Wichita, Kan.; Henry Hynes; 198; $87,998; 135 patients; SWOG.

• Central Los Angeles CCOP, St. Vincent Medical Center, Los Angeles; Armand Bouzaglou; 200; $56,079; 86 patients; SWOG, RTOG.

• St. Louis CCOP, St. John's Mercy Medical Center, St. Louis; Patrick Henry; 202; $55,098; 84 patients; SWOG, GOG.

• San Gabriel Valley CCOP, Huntington Memorial Hospital, Pasadena, Calif.; Michael Kadin; 204; $72,810; 112 patients; USC, SWOG, GITSG.

• Virginia Mason Research Center, Seattle, Wash.; Albert Einstein Jr.; 206; $58,888; 90 patients; SWOG.

• Kansas City CCOP, Baptist Memorial Hospital, Kansas City, Mo.; Robert Belt; 208; $61,648; 94 patients; SWOG, RTOG.

• Dayton CCOP, Kettering Medical Center, Kettering, Ohio; James Ungerleider; 213; $55,089; 84 patients; SWOG.

• Billings Interhospital Oncology Project; Billings, Mont.; Neel Hammond; 215; $43,324; 66 patients; SWOG, NSABP, Univ. of Arizona.

• Greater Hartford CCOP, Capital Area of Connecticut Community, Newington, Conn.; Dominick Pasquale; 218; $54,315; 83 patients; ECOG, GITSG, Yale.

• Overlook Hospital, Summit, N.J.; James Wolff; 218; $58,600; 90 patients; Columbia Univ.

• Des Moines General Hospital, Des Moines, Iowa; Fred Brunk; 218; $70,868; 109 patients; Mayo, CCSG.

• Medical Center CCOP Consortium, Newark Beth Israel Medical Center, Newark, N.J.; Frederick Cohen; 219; $99,098 152 patients; ECOG, NSABP, GITSG, MSK, CCSG.

• Southwind CCOP, Deaconess Hospital, Evansville, Ind.; Jack Williams; 219; $34,838; 53 patients; SEG.

• Greater Phoenix CCOP, Good Samaritan Medical Center, Phoenix, Ariz.; David King; 220; $55,915; 86 patients; SWOG, RTOG, CCSG.

• Sioux Falls Community Cancer Consortium, Univ. of South Dakota, Sioux Falls; Robert Marschke; 223; $93,970; 144 patients; NCCTG, ECOG, Mayo.

• Alton Ochsner Medical Foundation, New Orleans; Carl Kardinal; 226; $74,210; 114 patients; Univ. Alabama, SEG.

• Saint Mary of Nazareth Hospital Center, Chicago; Korathu Thomas; 228; $55,040; 84 patients; ECOG, Illinois Cancer Council.

• Presbyterian St. Luke's Cancer Study Group, Denver; Robert Berris; 231; $77,022; 118 patients; ECOG, RTOG, GITSG.

• New Engalnd Collaborative CCOP, New England Deaconess Hospital, Boston; Jacob Lokich; 232; $75,777; 116 patients; Lombardi, MAOP, GITSG.

• Kaiser Foundation Research Institute, Sacramento, Calif.; Scott Johnson; 234; $33,061; 50 patients; CCSG, Wilm's Tumor Study Group.

• Grand Rapids CCOP, Butterworth Hospital, Grand Rapids, Mich; Edward Moorhead; 235; $50,698; 77 patients; SWOG, Detroit, NSABP, RTOG.

• Carle Cancer Center CCOP, Carle Clinic Assn., Urbana, Ill.; Alan Hatfield; 236; $61,414; 98 patients; ECOG.

• Memphis Cooperative Community Oncology Program, Methodist Hospital Central Unit, Memphis, Tenn.; Ronald Lawson; 238; $36,798; 56 patients; SWOG, GITSG.

• Midwest CCOP, St. Luke's Hospital, Kansas City, Mo.; Karl Hanson; 239; $60,550; 93 patients; SWOG, NSABP.

• Lutheran Medical Center, Brooklyn; Hosny Selim; 245; $41,200; 63 patients; RTOG, MSK.

• St. Mary's Hospital, Rochester, N.Y.; Kishan Pandya; 247; $50,132; 77 patients; ECOG, Univ. of Rochester, Wisconsin Cancer Center.

• University Hospital, Augusta, Ga.; Stephen Shlaer; 247; $57,407; 88 patients; SEG, Medical College of Georgia.

The above were funded on the basis of their priority scores, with the cutoff at 247. Six more were funded as exceptions, with geography and perhaps other factors outweighing the scores. They are:

• Southern Nevada Cancer Research Foundation, Las Vegas; John Ellerton; 253; $60,672; 93 patients.

• West Virginia Cooperative CCOP, Charleston; Steven Jubelirer; 258; $56,262; 86 patients.

• Spartanburg CCOP, Spartanburg General Hospital, South Carolina; John McCulloch; 260; $47,838; 73 patients.

• Fargo Clinic, Fargo, N.D.; Lloyd Everson; 274; $121,517; 186 patients.

• Arkansas Oncology Clinic, Little Rock; Billy Tranum; 282; $32,720; 50 patients.

• Hawaii CCOP, Hawaii Medical Assn., Honolulu; Reginald Ho; $84,855; 130 patients.

Complete lists of research bases were not available for some CCOPs. Some of the abbreviations listed above: ECOG–Eastern Cooperative Oncology Group; CCSG–Childrens Cancer Study Group; NCCTG–North Central Cancer Treatment Group; SEG–Southeastern Cancer Study Group; CALGB–Cancer & Leukemia Group B; MAOP–Mid-Atlantic Oncology Program; POA–Piedmont Oncology Assn.; POG–Pediatric Oncology Group; SWOG–Southwest Oncology Group; GITSG–Gastrointestinal Tumor Study Group; GOG–Gynecologic Oncology Group; MSK–Memorial Sloan-Kettering.

DCBD BOARD OKs RECOMBINANT DNA DIAGNOSIS CONCEPT, TWO OTHERS

Three concepts were approved and three were rejected by the Board of Scientific Counselors of NCI's Div. of Cancer Biology & Diagnosis at the Board's meeting last month.

The Board approved unanimously the concept of a grants program for application of recombinant DNA technology to the diagnosis of cancer. Four grants will be awarded for three years each, at a total cost of $600,000 a year.

DCBD Director Alan Rabson said that the NCI Executive Committee "is very excited about this." Also, "In R01 applications, most people have been reluctant to mention recombinant DNA for diagnosis. The study sections do not look with favor on them." Thus, an RFA, with money set aside and earmarked for application of recombinant DNA to diagnosis, would assure funding of high quality applications.

Staff description of the proposal:

Scientists are using the tools of recombinant DNA technology to compare genetic information in normal and cancer cells. The techniques of restriction endonuclease analyses of DNA, nucleic acid hybridization after electrophoretic separation of nucleic acid fragments, and in situ hybridization with DNA probes for oncogenes are being widely used in cancer biology. There are exciting recent discoveries that suggest that the molecular basis of cancer may consist of activation of oncogenes. Scientists in several laboratories have found that some malignant cells have non-random chromosomal translocations that result in increased expression of oncogenes. In at least one case, there is a change in single base pair of the DNA sequence of a normal cellular gene that results in an altered gene that can "transform" NIH eTe cells in vitro. The possibility exists that certain genetic changes may be identified consistently in malignant cells but not in normal cells thereby having important implications for diagnosis.

This RFA should increase the search for new applications of recent advances in recombinant DNA technology directed at the diagnosis of patients with cancer and attempt to provide additional information for the classification of tumors beyond standard morphologic criteria.

Recent work utilizing recombinant DNA technology has shown changes in location, levels of expression and even the nucleic acid sequences of certain genes in cancer cells which are not found in their normal counterparts. These findings suggest that it may be possible to develop molecular approaches to the identification of malignant cells and thus improve the accuracy of cancer diagnosis.

The Board approved recompetition of the contract for radioimmunoassay and enzyme immunoassay of immunoglobulin molecules and antibody. The contract, which supports the division's Metabolism Branch, presently is held by Hazleton Laboratories.

The new contract will be awarded for three years, with total costs estimated at $200,000, $220,000, and $240,000 per year.

Staff description of the concept:

This contract is a recompetition of a contract to provide support for the performance of double antibody radioimmunoassays for immunoglobulin molecules using procedures established intramurally and using reagents provided by the intramural staff. These radioimmunoassays are an integral part of a major study of the Metabolism Branch on the terminal differentiation of B lymphocytes into cells synthesizing immunoglobulins, on the role of regulatory T cells and their products in this process and on the disorders of immune regulation in patients with immunodeficiency diseases and a high incidence of neoplasia and in patients with malignancy and associated immunodeficiency. This contract supports the research studies of the project officer, Thomas Waldmann, chief of the branch, and six other senior investigators in the branch: Michael Blaese, David Nelson, Warner Greene, Stanley Korsmeyer, Andrew Muchmore and Jay Berzofsky. In addition, the support services of this contract have been utilized by the Surgery Branch and by investigators in the National Institute of Allergy & Infectious Diseases.

To analyze the events of immunoglobulin regulation a series of techniques has been developed to study the terminal differentiation of B cells into immunoglobulin synthesizing and secreting cells, to study the role of macrophages in this differentiative process, to assess helper T cell function, and to detect both increased and decreased functional activities os suppressor effector T cells and their precursors and activators. For these studies, peripheral blood mononuclear cells are cultured in vitro in the presence of a polyclonal activator and at the termination of the study, the immunoglobulin produced and secreted by these cells are measured by sensitive radioimmunoassays specific for IgG, IgA, IgM and IgE. Assays for the subclasses of IgG and of IgA are being established. The studies are directed toward developing an understanding of the normal immune response as well as toward defining the nature of the regulatory defects in patients with primary and acquired immunological deficiency diseases (e.g., ataxia telangiectasia, agammaglobulinemia, selective IgA deficiency, acquired immunodeficiency disease); patients with immunodeficiency associated with malignancy (e.g., thymoma and hypogammaglobulinemia, multiple myeloma); patients with leukemias with retained immunoregulatory functions (e.g., Sezary helper cell leukemia and the human T-cell leukemia/lymphoma virus associated adult suppressor T-cell leukemia) and of patients with virus infections (e.g., Epstein-Barr virus infection). The radioimmunoassays are also used as the final step in which fractions obtained in the purification of soluble suppressor molecules are evaluated for their capacity to inhibit B-cell maturation and immunoglobulin synthesis. Our studies using recombinant DNA technology on the rearrangement of immunoglobulin genes that occur as a stem cell matures into a B cell require these radioimmunoassays as well as sensitive assays for lambda and kappa chains in order to identify the immunoglobulin chains present in pre-B and B-cell leukemias and lines and thus to define the nature of the clonal cells studied and their state of maturation. The in vitro cell cultures are performed intramurally while the support contract performs the radioimmunoassays using procedures and reagents developed intramurally.

The Metabolism Branch has developed antigen specific enzyme linked immunoabsorbant assays that can be used to quantitate specific antibodies in supernatants of short term cultures of human cells that are directed toward influenza virus antigens. These assays are used in studies of the regulation of the specific antibody response by human cells in vitro. These assays are being applied to disease states where immunoglobulins are produced, but where there are defects in specific antibody production (e.g., the Wiskott-Aldrich syndrome, ataxia telangiectasia, the antibody deficiency syndrome, etc.)

Since the Clinical Center has no central immunology laboratory, it is difficult to assess the capacity of patients with various malignant and immunodeficiency diseases to make a humoral immune response. In support of the Metabolism Branch clinical program, the contractor is to perform passive hemagglutinin assays and enzyme-linked immunoabsorbent assays for serum antibodies to protein and polysaccharide antigens on samples obtained from patients immunized with these antigens.

The contractor will be expected to perform 10,000 determinations in duplicate of IgG, IgA, IgM, IgE, kappa or lambda light chain, or IgG or IgA subclasses on supernatants of short-term cultures of mitogen stimulated mononuclear cells and on cell lysates yearly, using double antibody radioimmunoassay procedures according to the methods developed on the Metabolism Branch. The required reagents for these radioimmunoassays will be produced by Metabolism Branch personnel and provided to the contractor. Two thousand determinations of specific antibody to influenza A and B antigens will be performed by an established ELISA technique on supernatants of short term cultures of human peripheral blood cells that have been incubated with influenza organisms alone or with influenza organisms and pokeweed mitogen. This assay uses alkaline phosphatase linked anti-immunoglobulin as a developing probe.

Patients with various malignant and immunodeficiency diseases who are entered into NIH immunotherapy and chemotherapy protocols will be assessed for their capacity to make a humoral immune response by intramural personnel. The con-

tractor shall perform approximately 2,500 assays on submitted serum samples by already developed hemagglutination or ELISA techniques. The project officer will provide the antigens and standard positive and negative control sera.

The Board approved the concept of a noncompetitive renewal of the contract with the Mayo Clinic for the NCI serum diagnostic bank. Mayo has established and maintains a collection of frozen sera from patients with a variety of cancers and benign diseases and from healthy normal individuals. These sera are distributed to investigators as panels of coded specimens for evaluation of immunodiagnostic tests.

Renewal will be for five years, at an estimated annual cost of $190,000.

The Board rejected a concept for contracts to perform assays on multiple markers in ovarian cancer diagnosis. The proposal was for three contracts of two years each, to support three laboratories, at a total cost of $300,000 the first year and $200,000 the second.

The division last year awarded similar contracts for lung cancer markers. However, Board member Nelson Fausto commented, "Markers for lung cancer so far, including small cell, are not very good. My impression is that the available markers in ovarian cancer are not very good. I could see presenting this to the scientific community, and if there are two or three selected that look pretty good, and if you have a mathematical model, it could be useful. In the case of ovarian cancer, I don't think either condition is very good. You don't specify which markers, and you don't have the capability for analysis."

Robert McIntire, chief of the Diagnosis Branch, said that NCI's Biometry Branch would provide statistical support. "We could select the markers ourselves but felt we should take the best labs we could find, those best suited for this work, rather than choose the marker."

"There are so many unknowns," Board member John Stobo said. "There is no marker in the literature consistent with elevated levels in ovarian cancer. Now you are proposing to look at multiple markers. How will this contract solve that problem?"

McIntire said that the first phase of the contract would deal with that, asking for submission of sample panels.

The Board was not convinced, voting 5-3 to reject the concept, although suggesting that staff submit a revised proposal at the Board's next meeting. The Board suggested that NCI specify which markers would be used in the assays, and McIntire agreed.

The Board also rejected another concept proposed by the Diagnosis Branch, for development of monoclonal antibodies specific for tumor markers.

The project would have funded two grants, for three years, at a total estimated cost of $250,000 a year.

"Some work is going on (in that area) but we feel it needs some more stimulating," McIntire said. Board members Lisa Steiner and Stewart Sell commented on the "tremendous amount" of research being done with monoclonal antibodies, but McIntire argued that "relatively little is being done that is designed to make quantitative analysis of serum."

"That is true," Board Chairman Matthew Scharff said. "There are only a few. I did a literature search of those that actually did serum levels, and it was surprising. Everyone is in favor of this work being done. The question is, does it require an RFA?"

The vote to disapprove the concept was 4-2, with two abstentions.

The Board voted unanimously not to approve the concept of continuing the contract with Howard Univ. for the Morris hepatoma resource. The vote followed a staff recommendation to discontinue extramural contract support.

Harold Morris had developed the resource at Howard and was providing it to investigators under an R01 grant. In 1980, NIH decreed that since it was a resource, it should be supported through a contract. However, when the contract concept was presented to the DCBD Board, the members agreed that development of a cyropreservation technique required for quality maintenance of the tumors involved research and should be funded through a grant. Howard received a three year contract in 1981 to maintain and supply the tumors, but NIH refused to approve an RFA for the cryopreservation aspect, insisting it should be a contract.

NCI conducted a survey of Morris hepatoma users to assess its value. The conclusion:

"Much of the research being done requires comparability of results between experiments and we are seriously concerned as to the ability of these tumors to serve that purpose. Only a few of the evaluations we received were strongly positive or strongly negative, while most of the others presented equivocal opinions."

CONCEPT REVIEW FIGURES ARE ESTIMATES ONLY; RFPs, RFAs NOT YET AVAILABLE

The dollar estimates with each concept review brought before the various boards of scientific counselors are not intended to represent maximum or exact amounts which will be spent on those projects. They are intended only as guides for board members to help in determining the value of the projects in relation to resources available to the entire program or division. Responses should be based on the workscope and description of goals and methods included in the RFPs (contracts) and RFAs (grants and cooperative agreements). Availability of RFPs and RFAs will be announced when the Institute is ready to release them.

The options presented to the Board were to maintain the resource as a contract and include a cyropreservation component, or discontinue extramural contract support entirely. Staff recommended the latter, and the Board agreed.

Staff also recommended, and the Board concurred, that all users be encouraged to maintain their own tumors, and to seek administrative supplements to their NIH grants (those that have them) to maintain the tumors until renewal time.

RFA NCI-DCCP-BCB-83-3

Infectious Etiology of Acquired Immune Deficiency Syndrome (AIDS) and Kaposi's Sarcoma

Application Receipt Date: Aug. 1, 1983

The Div. of Cancer Cause & Prevention of NCI and the National Institute of Allergy & Infectious Diseases invite applications for cooperative agreements to support research projects into the microbiological etiology of acquired immune deficiency syndrome in humans. AIDS patients now include both homosexual and bisexual males, hetersexual intravenous drug users, hemophiliacs, Haitians and some infants. In addition to disorders of immunological function, approximately half of the AIDS victims suffer from pneumocystic carinee pneumonia and about one-third have Kaposi's sarcoma or lymphomas. The mortality rate is near 40 percent overall, but closer to 85 percent for cases diagnosed early in 1981. The long term prognosis for AIDS is very poor.

The recent involvement of hemophiliacs, apparently normal children, and some common epidemiological features now suggest a blood borne, venereal, or close contact transmissible biological agent as the causative factor. Two viruses, human cytomegalovrius (HCMV) and Epstein-Barr virus (EBV), have already been linked with AIDS, KS, and lymphomas. HCMV has been associated with KS by at least one molecularly oriented study of KS tissue, and EBV determined nuclear antigen has been demonstrated in tissues of several AIDS patients with a Burkitt's-like lymphoma. Further, several viruses have already been associated with certain human cancers: the etiological association of EBV with nasopharyngeal carcinoma; the papilloma viruses with malignancies of the skin, cervix and anus; HCMV with KS; and human T-cell leukemia-lymphoma virus (HTLV) with several malignancies. Recent advances in the study of cellular and viral oncogenes relative to cancer induction appear promising in ferreting out a basic mechanism of cancer induction. All these advances indicate that there is a rational basis for initiating systematic efforts to search for the transmissible agent presumed responsible for the AIDS syndrome and Kaposi's sarcoma.

Purpose of this RFA is to stimulate studies aimed at a direct microbiological approach to the problem. It is designed to encourage studies on the search for the isolation, and the characterization of the biological agent(s) which may be the primary causative factor(s) in AIDS and KS. The studies proposed should encompass not only the classical microbiological technologies for isolation and characterization of the agent, but also the contemporary technologies of immunology, cytogenetics, and molecular biology. Since HCMV and EBV, both transforming viruses, have been implicated in immune suppression and in association with KS and lymphomas, definitive studies of HCMV and EBV in terms of their relationship to the etiology of AIDS and KS would be considered as pertinent to the objectives of the RFA. However, it is emphasized that projects involving either or both RNA core or DNA core viruses, bacteria, rickettsia, or other potentially causative agents will be considered. Examples of the types of studies that might be appropriate include:

1. Direct in vivo and in vitro efforts at isolation, identification, and characterization of the causative biological agent.
2. Analysis of human tissue with appropriate tests indicative of the presence, state of integration, and location of viral or proviral DNA, or other infectious forms.
3. Recognition and identification of marker antigens of pathognomonic significance.
4. Cytogenetic analysis for chromosomal changes that relate to disease induction.
5. In vitro search for direct morphological transformation and/or cytopathology of appropriate target cells.

NCI and NIAID plan at least annual meetings of collaborating investigators funded under this RFA ("working group"). Collaborating investigators may constitute an independent working group or may become part of an already established AIDS working group. These annual or more frequent meetings of the working group will provide an opportunity for the development of collaborative arrangements between investigators performing complementary research. At this time it is impossible to explicitly outline the nature of such arrangements since the scope of projects to be funded is unknown. Typical arrangements may include the exchange of selected reagents, the exchange of certain human specimens, and/or the exchange of current information. NCI and NIAID will require these types of exchanges and will attempt to facilitate them. This cooperation will hasten the resolution of the important questions relevant to this epidemic and will result in a more effective allocation of funds. It is anticipated that NCI/NIAID staff will play a key role in coordinating and facilitating such collaborations as various research activities evolve by identifying data points. comparing protocols, comparing results, etc.

Because of the unknown nature of the disease, investigators will be required to utilize appropriate lab-

oratory control measures. Procedures should be used representative of good microbiological techniques applicable to the handling of materials containing hepatitis B virus or other infectious agents which may be transmitted by ingestion, parenteral inoculation, or exposure of mucous membranes to infectious droplets. As an additional precaution, it may be advisable to use a biological safety cabinet.

Awards will be made as cooperative agreements. These are assistance relationships involving substantial involvement with NCI/NIAID staff. NCI and NIAID anticipate making multiple awards as a result of this request. Up to $2 million ($1 million each by NCI and NIAID) will be allocated to fund the initial year's awards for meritorious applications. Awards will be made for project periods of up to five years.

Applications must be submitted on form PHS 398, the application form for research grants. Application kits are available at most institutional business offices, or may be obtained from the DRG, NIH. Since NCI and NIAID plan at least an annual meeting of the working group, applicants are encouraged to include in their budget travel funds for the principal investigator to attend at least one meeting per year in Bethesda, Md.

The completed original application and six exact copies should be sent or delivered to Div. of Research Grants, NIH, Westwood Bldg. Rm. 240, 5333 Westbard Ave., Bethesda, Md. 20205.

Additional copies (one each) should be sent to Dr. Jack Gruber, Biological Carcinogenesis Branch, DCCP, NCI, Landow Bldg. Rm. 9A22, Bethesda, Md. 20205, phone 301-496-9740; Dr. William P. Allen, Virology Program Officer, BVB/MIDP, NIAID, Westwood Bldg. Rm. 736, Bethesda, Md. 20205, phone 301-496-7453; and Dr. Harold Waters, Div. of Research Grants, NIH, Westwood Bldg. Rm. 2A16, Bethesda, Md. 20205.

Inquiries may be directed to Gruber or Allen.

RFA NCI-DRCCA-CPB 83-1

The Role of Micro and Macronutrients in the Prevention of Cancer

Letter of Intent Receipt Date: July 1, 1983
Application Receipt Date: Aug. 1, 1983

The Div. of Resources, Centers & Community Activities, NCI, invites applications for cooperative agreements to support risk reduction clinical trials which are directed at examining the role of micro and macronutrients in the prevention of cancer.

The proposed studies should seek to elucidate further the protective effects of inhibitors or of dietary prescriptions in reducing the incidence of cancers of specific sites.

Epidemiologic studies and laboratory research results support the concept that the incidence of cancer may be influenced by the levels of various nutrients and nonnutritive substances in the diet. A number of natural micronutrients including vitamin C, beta carotene, vitamin A or its analogs, selenium and alpha tocopherol have been associated, in animals or test systems, with the inhibition of carcinogenesis or have been associated with reduced cancer incidence, in epidemiological investigations.

The level of dietary fat has shown a positive correlation with incidence of cancer of several sites while increased fiber intake has shown a negative correlation with the incidence of cancer at several sites. A number of mechanisms has been postulated including increased detoxification of carcinogens, alteration of metabolism by decreased activation, scavenging of the active molecular species, prevention of the carcinogenic agent from reaching the critical target in the cell, altering permeability or transport, and competitive inhibition. Other possible mechanisms include antagonism of promoting agents or induction of differentiation of malignant cells.

Because of the numerous reports concerning the effectiveness of dietary manipulation or the administration of certain compounds in interfering with carcinogenesis in animals and the many epidemiological studies suggesting a possible negative assocation of certain dietary factors with cancer incidence, clinical intervention studies are now encouraged.

Purpose of this RFA is to solicit applications from qualified investigators interested in developing and implementing randomized controlled clinical trials to study the effect of micro or macronutrients on cancer risks in humans. Micronutrients include, but are not limited to the following: Beta carotene, vitamin A or analogs, vitamin C, selenium and alpha tocopherol. In addition, intervention trials involving several macronutrients including fats, vegetables, fruits, cereals and fibers will be considered.

This RFA is limited to clinical trials but excludes focus on skin cancer as the study endpoint with the exception of melanoma.

The studies of interest are risk reduction clinical trials involving (a) normal populations, (b) populations known to be at increased risk but free of neoplasia, or (c) high risk populations with identified precursor or precancerous lesions. These studies would require the administration of the designated inhibitors or dietary prescriptions in a randomized study with followup to determine the effects. Proposals involving studies of populations already having neoplastic lesions are not acceptable within the scope of this RFA.

Several items with regard to the proposal itself are provided as follows:

1. The applicant is encouraged, wherever germane, to focus attention on a specific target group, or to identify a source of participants and to address the methodological, organization, and theoretical issues in a detailed manner.

2. The applicant should provide a description of the target population or group chosen and should justify the selection of this group. The group should be defined, where appropriate, by age, sex, race, socioeconomic status, dietary customs, education, geographic location, occupational or life style risk factors, and relevancy to a specific cancer problem and to its possible prevention by designated inhibitors or dietary manipulations.

3. The applicant should specify the methods to be used to document nutrient intake at baseline and adherence to the prescribed intervention during the course of the trial.

4. The applicant should clearly indicate the clinical chemistry and biologic aspects of the study to include collection, storage, handling and analysis of biological samples. The methods and equipment to be utilized and the technical qualifications and experience of the personnel involved must be addressed.

5. The applicant should elucidate any known or potential safety or toxicity considerations, the techniques and procedures for monitoring and reporting any adverse health effects and appropriate dose modifications based on toxicity monitoring.

6. The applicant must indicate his agreement to work cooperatively with NCI staff in the implementation and conduct of the study.

Awards will be made as cooperative agreements. The total project period for applications submitted in response to this RFA should not exceed five years. The intent is to fund projects of high scientific merit, with total costs amounting to $3 million per year.

Awardees will develop a proposal based on their past experience, research interests, and information generated through pilot projects. The protocol shall be clearly written, well documented, and appropriately annotated for background, objectives, eligibility criteria, treatment administration, statistical considerations, and quality control.

Safety and toxicity aspects of the peer reviewed, approved, high priority proposals will be reviewed by an NCI staff committee chaired by the associate director, Prevention Program, DRCCA, or his designee. The primary purposes of this review are (1) to ensure that safety and toxicity issues have been addressed, and (2) to assure that the proposed research is in compliance with all FDA requirements and approvals. NCI staff will follow up on these recommendations to ensure adequate safety and compliance.

Awardees are expected to set up mechanisms for quality control. Quality control will require some or all of the following as relevant: compliance with protocol requirements for eligiblity, treatment and followup; laboratory data; dietary data; pathological materials; and operative reports.

For chemopreventive agents, investigators are required to conform to NCI guidelines for use of investigational drugs including investigator registration (Form 1573), maintaining a record of drug receipt and reporting of adverse drug reactions. Life threatening or unexpected toxicity must be reported by the investigator immediately by telephone to NCI and confirmed with details in writing within two weeks. The investigator will be responsible for amending protocols and consent forms based on new toxicity information sent to the investigators by NCI staff. NCI staff has developed mechanisms for prompt reporting to other investigators of all unexpected or serious toxicity caused by IND agents.

NCI staff is responsible for assuring the adequacy of safety monitoring and qulaity control for all chemopreventive studies involving NCI sponsored IND drugs. NCI staff will review the mechanism established by each applicant for quality control of clinical studies. These mechanisms must conform with FDA regulations.

NCI is establishing a clinical chemistry quality assurance program which will provide guidance in the quality control of selected laboratory determinations. Each applicant will be expected to participate in the laboratory quality control activity if applicable.

Prospective applicants are asked to contact program staff by telephone or to submit a one page letter of intent which includes a very brief synopsis of proposed areas of research and identification of any other participating institutions. This telephone contact or letter of intent should be addressed to Dr. Winfred Malone. The institute requests such contact to provide an indication of the number and the scope of applications to be recieved and for the purposes of identification of overlap and/or redundancy with currently funded research. The letter of intent is not binding; it will not enter into the review of any proposal subsequently submitted, nor is it a mandatory requirement for the submission of the application.

Applications must be submitted on Form PHS 398, the application form for research project grants. The completed original application and six copies should be sent or delivered to Div. of Research Grants, NIH, Westwood Bldg. Rm. 240, 5333 Westbard Ave., Bethesda, Md. 20205.

A copy of the application should also be sent to Winfred F. Malone, PhD, MPH, Chemoprevention Branch, Blair Bldg. Rm. 624, NCI, Bethesda, Md. 20205, phone 301-427-8648.

The Cancer Letter _Editor Jerry D. Boyd

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