THE CANCER LETTER

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CARTER ACCEPTS UPTON'S RESIGNATION EFFECTIVE DEC. 31; DEVITA ACTING DIRECTOR; SEARCH COMMITTEE FORMED

President Carter has accepted Arthur Upton's resignation as NCI director effective Dec. 31, when Upton will leave to become director of the Institute of Environmental Medicine at New York Univ. Div. of Cancer Treatment Director Vincent DeVita has been named acting director of NCI while a search committee begins the task of finding a permanent head of the institute and National Cancer Program.

It is possible that DeVita's tenure as acting director will stretch out well over a year. HHS search committees do not move very fast anyway, and with the election coming up, it does not seem too likely that a person with the credentials the job requires would accept a Presidential appointment until after next November—unless the offer were to be made to someone already at NCI would could go back to his former job if a new President decided he wanted to make his own appoint-

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In Brief

NEW RFAs, PROGRAM ANNOUNCEMENTS COMING UP SOON FROM BCDB FOR RADIATION, BREAST CANCER STUDIES

WATCH FOR new RFAs (request for applications) and program announcements to be released soon by NCI's Div. of Cancer Biology & Diagnosis. DCBD Director Alan Rabson told the National Cancer Advisory Board last week that an RFA will be released in January for studies to determine the biological effects of diagnostic levels of radiation. "We're looking for quick answers in animal studies," Rabson said. Jane Taylor, chief of DCBD's Breast Cancer Program Coordinating Branch, said there also will be two program announcements and an RFA for breast cancer studies in basic biology, diagnosis, epidemiology, treatment, and possibly prevention. . . . **BAYARD MORRISON**, NCI assistant director, is in Johns Hopkins Hospital where he is recovering from surgery to repair a detached retina. . . . **COOPERATIVE GROUP** chairmen's semiannual meeting scheduled for Dec. 13 has been canceled; too many chairmen said they couldn't make it. . . . **"WORKSHOP ON** Fat and Cancer" sponsored by NCI will be held at the Bethesda Marriott Dec. 10-12. . . . **TIM LEE CARTER**, top ranking Republican on the House Health Subcommittee and one of the architects of the National Cancer Act of 1971, will retire at the end of his term in 1980. A Kentucky M.D., Carter was elected to Congress in 1964, was immediately named to the Health Subcommittee, and worked with former Chairman Paul Rogers in a bipartisan effort that produced landmark health legislation. . . . **NATIONAL CANCER** Advisory Board's annual report in 1981 should undertake to show, on the 10th anniversary of the National Cancer Act, that the Cancer Program "has made a difference," the Board's Subcommittee on Board Activities recommended.

DEVITA NAMED ACTING NCI DIRECTOR; SCHEPARTZ INTERIM CHIEF OF DCT

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ment. DeVita undoubtedly will be one of the search committee's prime prospects.

That committee will be headed by the new HHS Undersecretary Nathan Stark. It will include Julius Richmond, surgeon general and assistant secretary for health; and NIH Director Donald Fredrickson.

Saul Schepartz, deputy DCT director, will move up to acting director of the division.

Carter, in accepting "with regret" Upton's resignation, said it was "a source of pride" that his administration has "attracted such talented people" as Upton to its service. He promised to continue the struggle against cancer.

Upton in his letter of resignation thanked the President for his support; noted that among the important contributions Carter has made were his recognition of the need for continued strong support of basic research; praised NCI's "outstanding" staff; and said the only reason he was resigning was because of a "special opportunity to return to the academic world" as director of the Institute of Environmental Medicine.

Norton Nelson, present head of that institute, had expressed his desire to retire from that position quite some time ago.

DeVita, 44, was appointed director of DCT in 1974 after Gordon Zubrod retired, moving up from his position as chief of the Medicine Branch. He was also named NCI clinical director and has held both positions since that time. A graduate of the College of William & Mary, he received his M.D. from George Washington Univ. and joined NCI in 1963 as a clinical associate. He has played a key role in the development of chemotherapy as an effective modality against cancer and won wide acclaim for research in treatment of Hodgkin's disease with drugs.

DeVita took over DCT when it was in considerable turmoil, in the midst of transition from its former status as the chemotherapy division to that of responsibility for all treatment modalities. Surgery, radiotherapy and Cooperative Group programs were all located in other divisions; when they were moved to DCT, there was considerable apprehension and some resentment. It could have been an organizational nightmare.

DeVita made the tough decisions, moved some people out, encouraged the phasing out of the less effective Cooperative Groups, fought for and received more money for them, reshaped the DCT structure to meet the broader mandate and later shepherded the division through Upton's massive reorganization, and managed to win over just about everyone involved. He has turned out to be a superb administrator and an effective and articulate representative of DCT and NCI when called upon.

Upton became director of NCI in 1977, 10 months after Frank Rauscher resigned. Guy Newell, Rauscher's deputy, had served as acting director in the interim.

Upton's credentials were largely that of a scientist rather than an administrator, but he quickly demonstrated that he had no qualms about making profound administrative changes. His reorganization was perhaps the most far reaching in the institute's history. It gave the program divisions the responsibility for managing grants as well as their extramural contracts (hopefully ending at last the age old grants vs. contracts argument); it reduced the emphasis on research contracts and increased support of investigator initiated research; it separated program activities from review of extramural programs; it may have formed the basis for more effective coordination and cooperation between the Centers and Cancer Control Programs.

Upton has been able to convince most of NCI's prevention-minded critics that the institute does support a significant amount of prevention research and that that support is increasing, without decreasing support of treatment related activities.

COMPETING CORE, P01 GRANTS GET HELP FROM NCI "SEVEN PERCENT SOLUTION"

At NCI, they're calling it "the seven percent solution." At a number of cancer centers and other institutions where core grants and program project grants were competing for renewals this year, they may have a term for it that is less complimentary and perhaps unprintable.

"The 7% solution" is the method by which NCI plans to make up for the huge deficits which have turned up in the FY 1980 budgets for cancer center core grants and program projects—deficits which would leave some very good centers and some very worthwhile program projects without their grants if additional money is not found.

Here is the situation:

• Thirteen cancer center core grants are up for renewal this year (actually, 12 existing center core grants and one that is being transferred from a program project to a center grant). There also is one new core grant that will be reviewed later this year. The NCI 1980 budget for center core grants is somewhat less than it was for 1979—$63.5 million, compared to $64.4 million. Ten of the competing renewals have been reviewed and approved, at funding levels which indicate that if the remaining four are approved at comparable levels, the money available will be $7-8 million short of paying all 14 at the recommended levels.

• Twenty-three program projects up for renewal this year and one new P01 have been reviewed and approved at levels that, with the money originally budgeted, could have left as many as 15 of them unfunded.

NCI Director Arthur Upton and his senior staff decided it would be unacceptable to wipe out support for such an important segment of the Cancer Program. Various commitments and congressional mandates left them with very little discretionary money which could be reprogrammed. They concluded that the only way to help make up the difference was to limit the core grant and program project renewals to a 7% cost of living increase over their current levels of support. Here's what that would accomplish:

—It would reduce the shortfall in the Centers Program from $7-8 million to $2 million and perhaps less. Upton probably can squeeze that amount out of his director's reserve and perhaps elsewhere, which would permit funding of all 14 (depending, of course, on how the remaining four fare in review).

—It would permit the funding of 19 of the program project renewals, with some prospect of paying as many as four more from additional money that might be found elsewhere.

More program projects are scheduled for review prior to the May meeting of the National Cancer Advisory Board; it is possible that the crunch will become worse.

NCI expects at least three of the four center core grants still to be reviewed to do very well and thus be considered among those that must continue to receive support. The fourth could also be in that category.

The Div. of Cancer Treatment has the most serious problem, with 11 clinical program projects reviewed and approved and money originally available only to fund two of them. The DCT Board of Scientific Counselors went along with transferring $700,000 from the $1.6 million budgeted for surgical oncology grants to program projects (***The Cancer Letter,*** Nov. 2). That would pay two more of the program project renewals. The 7% solution would make enough money available to fund three more, leaving four clinical projects still unfunded. John MacDonald, director of the Cancer Therapy Evaluation Program, still hopes enough money can be found elsewhere in DCT to pick up some of those four, if not all.

The crunch wasn't quite as bad in the other divisions. The Div. of Cancer Cause & Prevention had seven program projects which were approved. One of them had a low priority score, 289, and probably would not be funded in any case. DCCP had enough in the budget to pay four of the others, and the 7% rule would pick up another. A sixth will be paid from discretionary funds made available through phasing out of contracts. One of the six was a new grant which competed very well, with a score of 210.

The Div. of Cancer Biology & Diagnosis had six up for renewal, three in tumor biology and three in immunology. The 7% solution will permit all to be funded, but Ihor Masnyk, director of the division's Extramural Research Program, said "it is possible we will have a big problem in May."

The 7% solution will not be looked upon with favor anywhere except those centers and projects which, without it, would have ended up empty handed. When a similar limit was last applied, three years ago, it stimulated the American Assn. of Cancer Institutes to ask NCI in the future to pay core grants at recommended levels, regardless of how many that may leave unfunded. That same AACI recommendation said that new applications should be considered along with the competing renewals and funded on the basis of their priority scores.

Is AACI standing by its position, demanding full funding as far as the money will go?

"Our position is that the National Cancer Advisory Board has asked Dr. Upton to find the money to permit approved grants to be funded at the peer review recommended levels, and he has agreed to try to do that," AACI President Gerald Murphy told ***The Cancer Letter.*** The NCAB did approve such a resolution last week, but Upton did not promise anything except the effort. It does not seem likely that NCI would impose a 7% limit on program projects and lift it for center grants, even if the money could be found. It is less likely that enough could be found to fully fund both P01s and center grants.

The problem is made excruciating by the fact that, without additional money, centers and projects which scored extremely well in review would be left unfunded. Scores of most of the center core grants were around 200; at the original budget, one would go unfunded which had scored in the 190s.

It was the same story in the program projects. The original cutoff with the DCCP grants was 206, which would have funded four. The other two which will be funded came in at 212 and 222.

NCAB member Denman Hammond pushed the resolution through the Board asking Upton to try to find more money for centers. Previously, at a meeting of the Board's Subcommittee on Planning & Budget, Hammond had severely criticized NCI for not budget-

ing at least a cost of living increase for the Centers Program.

In NCI's budget submitted to the White House, for a total of $1.037 billion, there was an increase for centers. The President's budget that went to Congress, however, cut everything back to 1979 levels, totaling $937 million. Congress increased the total to $1 billion but earmarked every dime of the extra money, with none of it going to centers.

The earmarks were in response to effective presentations made to the House and Senate Appropriations Committees by advocates of increased support for basic research, biological response modifiers, carcinogenesis testing, community cancer control programs.

Center representatives probably could have had the same success had they made a pitch on their own behalf. When the appropriations hearings were held last spring, however, the extent of the problem was not yet evident. Centers people and NCI staff knew the core grant budget would be short but counted on the usual increase Congress makes over the President's request. What they didn't count on was the inflexibility that increase would take on this year.

NEW GUIDELINES FOR RECOGNITION OF COMPREHENSIVE CENTERS APPROVED

The National Cancer Advisory Board overcame a strong urge to nitpick and finally adopted the new guidelines for recognition of a cancer center as comprehensive.

The new guidelines replace the "10 characteristics" of comprehensive centers written by the NCAB when the practice of NCI recognition of centers as "comprehensive" began in 1972.

The primary requirements remain: high quality multidisciplinary basic and clinical research, and regional leadership in outreach programs including including training and education. Those activities are somewhat more clearly defined in the new guidelines.

One major addition is the requirement that centers must have a funded NCI core grant to be considered for comprehensive recognition. Another is that they must demonstrate they have "material support" from parent institutions and communities.

Another new requirement has turned out to be somewhat controversial—that comprehensive centers must participate in uniform clinical data acquisition and reporting through the Centralized Cancer Patient Data System.

Twenty of the 21 comprehensive centers have grants supporting CCPDS development. The Univ. of Southern California center does not but is still supplying uniform information. M.D. Anderson has a CCPDS grant but until recently balked at providing information in the CCPDS format.

NCAB member Denman Hammond, director of the USC center, expressed his and MDA's objection to the requirement. Some have felt it inappropriate that funding was through research grants, Hammond said, and others thought that other better systems might be developed "next year or the year after."

Centers Program Director William Terry said many institutions have found the common data set useful for their own activities. "I don't understand the objection," he said.

Hammond withdrew his motion to drop the CCPDS requirement when it was obvious other Board members were not swayed by his arguments.

The Board made only minor changes in the document that was submitted to it in October. Examples of research areas which would not necessarily have to be pursued at all centers were dropped from the preamble. Requirements that centers serve as "primary focal points" for cancer control and training, education and information dissemination were changed to "important focal points." The preamble statement which said "the NCAB does not intend that *any* institution participate in all possible activities relevant to cancer" was changed to *every* institution.

The new guidelines, as adopted by the NCAB:

These guidelines describe the qualities and characteristics that the National Cancer Advisory Board considers essential for recognition of a cancer center as comprehensive. They will be used by reviewers to evaluate centers that are seeking recognition as new comprehensive centers and also to evaluate established centers to determine the advisability of continued recognition.

In establishing these guidelines, the NCAB does not intend that every institution participate in all possible activities relevant to cancer. For example, although one of the requirements for recognition as comprehensive is the existence of high quality research activities, there is no requirement that all research areas be pursued at a given center. Rather , there is the requirement that there be high quality activity in some aspects of clinical research, some aspects of laboratory research, some aspects of cancer control, and some aspects of training, education, and information dissemination. The term comprehensive is intended to convey that the cancer center has high quality activities in each of these major areas, but that within any given area, the center may choose to pursue particular topics and not others.

1. National and Local Support

The cancer center must have a funded Cancer Center Support (Core) Grant, indiciating that center activities are of sufficient quality to achieve funding from the National Cancer Program. In addition, there must be evidence of material support for center activities from the parent institution(s) and the local community.

2. Research Activities

The cancer center should support laboratory, clinical, epidemiologic, and evaluative research efforts of the highest quality and should create an environment which fosters cancer-related information exchange, cooperation, and collaboration between laboratory scientists of multiple disciplines and between laboratory scientists, clinical scientists, and epidemiologists. Centers should maintain their own clinical investigative activities. (Those activities should include participation in regional and/or national clinical trials related to the cancers being studied by the center in question. The center should have available the personnel and facilities to carry out high quality diagnostic, therapeutic, and rehabilitative procedures in the interdisciplinary setting most suited to the cancers being investigated.) The center should make a commitment to participate in uniform clinical data acquisition and reporting through the Centralized Cancer Patient Data System (CCPDS).

3. Cancer Control Activities

The cancer center should serve as an important focal point for local and regional programs designed to control cancer through research and demonstration activities in areas such as prevention, detection, diagnosis, treatment, and rehabilitation. The center should seek the active participation of all sectors of the professional and lay community in control activities.

4. Training, Education, and Information Dissemination

The cancer center should serve as an important focal point for local and regional information dissemination, as well as for professional and lay education programs. Programs to assess which methods of information dissemination and education effectively modify professional and lay behavior patterns are desirable. Centers should also be actively involved in training of professional and support personnel.

5. Administration

The cancer center (or in the case of consortia, the constituent institutions) should have a formal commitment of support from the parent institution(s), manifested by the center director having the following: (a) primary control of space and equipment, (b) necessary control over professional and staff appointments to enable the center director to effectively direct the center and assure accomplishment of its mission, (c) control of grouped beds and ambulatory facilities for (clinical) cancer research, and (d) responsibility for program planning, evaluation, and (implementation), preparation of budgets and control of expenditures. In addition, the center must have an administrative structure that will assure long-term viability, efficiency of operation, and sound financial practice.

6. Geographic Impact

Scientific excellence of any center is a primary consideration. The geographic location of the cancer center, however, should increase the national capability to carry out regional clinical trials, regional cancer control programs and regional training, education and information dissemination activities. The location of other comprehensive centers and the size of the regional population with access to the center are additional factors bearing on recognition.

NCI DEVELOPS FORMAL GUIDELINES FOR INSTITUTIONAL TRAINING GRANTS

NCI has developed a set of guidelines for its $23 million research training grant program which Research Manpower Branch Chief Barney Lepovetsky said "formalizes" policy that has been generally followed in the past. Some institutions with training grants have not always followed the rather loosely stated policy, however, so NCI decided to present grantees and applicants with a written set of guidelines.

A statement delivered to the National Cancer Advisory Board by Lepovetsky said:

"Cancer is a complex of diseases which will be understood only after many more years of basic and applied research in all areas of biomedical science. To assure an adequate number of gifted researchers for an effort of this breadth, NCI maintains a stable, long term research training system whose scope includes all relevant clinical and nonclinical sciences. The principal criterion for funding research training projects is quality of the training. Implicit in that term is the requirement that a scientist training in a discipline be exceedingly well trained in that discipline.

"Secondarily, the trainee should be oriented towards cancer during the course of training so that in the future he will be able to relate the skills and tools of his scientific discipline to the ultimate understanding of cancer. So that the best and most responsive kind of training will be offered, NCI's training system encourages each research institution to use its own unique strengths in building its cancer research training program. Some institutions will do their best with small unidisciplinary programs; others will capitalize on the diversity of their strengths and will develop excellent highly multidisciplinary programs.

"To assure that NCI's research training system will continue to develop in accord with these concepts, the following policies will be followed in the review of applications and in the administration of the program:

"1. It is not mandatory that a trainee engage in research palpably related to cancer, nor that his preceptor be engaged in such research. However, the reviewers will take note of the following questions in assessing the merit of research training grant applications:

"a) Will each predoctoral trainee attend a general course concerning the cause, nature, diagnosis and treatment of cancer?

"b) Are more specific courses also available to predoctoral trainees, as, for instance, tumor virology, tumor immunology, etc.?

"c) Will predoctoral and postdoctoral trainees attend cancer-related seminars, journal clubs, or lectures on a regular basis?

"d) Will postdoctoral trainees deficient in oncologic knowledge have access to the resources mentioned in 'a' and 'b' above?

"All trainees and fellows will be encouraged to attend one NCI-sponsored 'Pathobiology of Cancer Workshop' during their training period. Research training projects embodying the above features will be deemed to show 'cancer orientation'.

"2. To allow NCI to take advantage of strengths unique to each training site, applicants are to be afforded maximum freedom in shaping high quality training projects. Therefore the following is permitted as a matter of policy:

"a) More than one training grant per division, college or campus.

"b) Overlap in the disciplines covered by several grants to one institution, provided the training offered is of high quality.

"c) Overlap in faculty, provided faculty members are not overburdened with training responsibilities to a project's detriment."

These guidelines apply only to the institutional training grant program. In the current 1980 fiscal year, the $23 million will support 150 grants which involve about 1,050 trainees. Individual fellowships, for postdoctoral training only (training grants are both pre- and postdoctoral), will total about 250

MIHICH SUBCOMMITTEE RECOMMENDATIONS FOR AUGMENTING AGENTS IN BRMP LISTED

The report of the Mihich subcommittee of the NCI Div. of Cancer Treatment Board of Scientific Counselors on development of the Biological Response Modifiers Program included a section on augmenting agents. The summary of the subcommittee's recommendations for augmenting agents follows (other recommendations appeared in the Nov. 9, 16 and 30 issues of ***The Cancer Letter***):

Augmenting agents can be defined as including those natural or synthetic products which increase above the normal resting level the immune or host defense reactivity of the subject. This area included the so called active nonspecific immunotherapeutic agents, the microbial adjuvants, a variety of low and high molecular weight polymers, interferon inducers and certain other compounds.

The interim review of this area has resulted in identification of a group of agents of interest which have antitumor activity in animal models, which modify biological response in a measurable fashion and for which monitoring methodology is available for clinical trials. One agent has been selected for initial development and is indicated below. Other agents of interest will be considered and should enter the program by operation plan outlined in this report.

Specific proposal for the development of an augmenting agent during the initial period of the BRM Program.

a. Background statement

Recently a variety of synthetic augmenting agents have been developed which, at least in animal models, have shown considerable promise for the development of their use in immunotherapy of human cancer. In addition to this, recent immunological developments including an improved understanding of the human immune response and the development of good assays to monitor monocyte and macrophage activation and activation of other defense mechanisms will permit the clinical development of these agents in a rational fashion. This should overcome some of the difficulties experienced in earlier work with augmenting agents in which appropriate monitoring was either not available or not applied. There are a large number of augmenting agents and interferon inducers which have activity in animal tumor models and measurable biological response modifying activity. Priority selection on the basis of efficacy data is very difficult. Nevertheless, one agent was selected for the BRM development network, the study of which in a phase 1 trial will establish the mechanism by which an augmenting agent can be evaluated for its biological activity in man. The utility of the general phase 1 experimental design and host defense mechanism evaluation techniques will be evaluated during this first year's work.

The agent recommended for the first year is MVE-2. This is the 15,500 molecular weight copolymer of maleic anhydride and divinyl ether and is related to the parent compound pyran copolymer. Pyran copolymer has shown antitumor activity in a variety of animal models and in addition was used clinically in phase 1 trials. However, it proved highly toxic, presumably because of its heterogeneous molecular weight and content of higher molecular weight components. MVE-2 is highly purified and of defined molecular weight and in animal models has been shown to be active with markedly reduced toxicity. Preclinical toxicology studies have been conducted by Adria Laboratories and an IND is about to be filed. In addition to MVE-2, a spectrum of MVE compounds, MVE-1 through MVE-5 with a spectrum of molecular weights is available for future investigation. Clinical investigation of these agents should await the results of phase 1 trials with MVE-2 which is the lowest molecular weight fraction with biological activity.

b. Description of agent

MVE-2 is the linear copolymer of maleic anhydride and divinyl either. It is highly anionic, water soluble, and has a molecular weight of 15,500. On intravenous administration it is taken up by and localized in the monocyte-macrophage RES compartment and 20% of the activity of an injected dose persists at five weeks. The mechanism of action is independent of interferon induction, although this does occur, and is most closely related to long lasting macrophage and NK cell activation. Toxicity, side effects and untowards reactions to be expected would include hepatosplenomegaly, inhibition of hepatic mixed function oxidases, heparin-like anticoagulant activity, potential activation of suppressor T-cells and clinically, fever, chills, and impaired liver or renal function. The above is based on observations of pyran, and it has already been demonstrated in animals that MVE-2 is much less toxic. The LD 10 dose of MVE-2 in the mouse is 100 mg/kg which translates to approximately 300 mg/m^2 in man. In the early studies of Regelson with pyran, 12 mg/kg was toxic but not lethal and this translates to approximately 440 mg/m^2.

c. Recommendations for phase 1 trials

It is recommended that three independent groups carry out phase 1 trials with this agent. The phase 1 trials should be carried out in patients with advanced, chemotherapy refractory malignant disease of known limited life expectancy, who are however, in satisfactory clinical condition so that they are likely to respond to biological stimulation. Thus, patients with severe immunodeficiency would not be candidates. Dose escalation should begin at 1/10 of the above described doses of 300-400 mg/m^2 and intervals of treatment might range from weekly with careful escalation to daily administration.

d. Recommended monitoring

Clinical monitoring should include acute studies

of cardiovascular status and serial studies of pulmonary, hepatic, renal function and hematological function. Attempts should be made to study the pharmacology of the agent with radiolabeled compounds which will be available from Adria Laboratories. Host defense monitoring is mandatory. This should include pretreatment evaluation of general immunocompetence with delayed hypersensitivity, leukocyte subpopulation enumeration, and lymphocyte blastogenesis. Before and during treatment monitoring for biological response modification should include measurement of interferon induction, NK cells, ADCC, monocyte mediated cytotoxicity, monocyte precursor numbers in the peripheral blood, serum lysozyme, and if possible, RES clearance of particulate matter. Evidence for optimal biological response modification will be the data base on which to develop phase 2-3 clinical trials.

e. Future developments

The three phase 1 trials of MVE-2 should establish whether the material is active as a biological response modifier in man. If an optimal biologically stimulating dose is defined with acceptable toxicity, this should result in phase 2-3 studies. These should be started during the second to third year of the program. In addition, the phase 1 studies of MVE-2 should establish a rational clinical immunological approach to the evaluation and development of other augmenting agents. With the establishment of this mechanism, it should be possible later in the program to carry out phase 1 studies of other promising augmenting agents such as MVE-4, poly IC with mismatched bases, lipoidal amines, NED137, low molecular weight interferon inducers, glucan and other polysaccarides, etc. These compounds will be introduced into the program according to the operational scheme. This will be the major objective and hopefully the major achievement of the first year's program.]

Augmenting Agents Considered at This Time of Interest for Development through the Biological Response Program

a. Natural products—1. mycobacterial, MDP (muramyl dipeptide derivatives), BCG cell wall fractions. 2. polysaccharides, glucan and dirocan, tentinan, bestatin. 3. endotoxins.

b. Synthetic polymers—1. anionic polymers, MVE-2, MVE-4. 2. neutral polymers. 3. lipoidal amines. 4. polynucleotides.

c. Low molecular weight interferon inducers.

d. Azuridine dye derivatives.

The above list is based primarily on the availability of data regarding efficacy in animal models and preclinical toxicity data. Thus, MVE-2 and MVE-4 have antitumor activity but considerably less toxicity than crude pyran copolymer from which they are derived. For example, nontoxic doses can cause regression of the Madison 109 tumor. Polynucleotides are potentially important but several are highly toxic. Poly IC with mismatched bases is a very potent interferon inducer with markedly reduced toxicity because of its short half-life and rapid catabolism. The above are ready for clinical trial and related compounds have already been given to man. There are several lipoidal amines which are macrophage and RES activators, some of which are also interferon inducers and others which are not. These have been shown to prevent recurrence of animal tumors after surgery and are now in preclinical toxicology study.

A low molecular weight polymer (not an interferon inducer) which prevents recurrence or metastatis after tumor surgery in animals (NED-137) is in clinical trials in Canada and is undergoing preclinical toxicology study. Several pharmaceutical firms have low molecular weight interferon inducers under development but their potential role in cancer therapy is unclear. This most important potential role may be for their potential synergism with interferon itself. Selection of agents and priorities will be based on preclinical data according to the development tracks outlined in this report.

Confirmatory Clinical Therapeutic Trials of Augmenting Agents

While a large number of therapeutic trials of augmenting agents has been conducted in patients with various types of cancer, it is often difficult to reach firm conclusions as to the efficacy of these agents for several reasons. They include deficiencies in trial design, conflicting results of comparable trials, lack of confirmation of formal trials, and lack of formal trials substantiating provocative anecdotal reports. For these reasons, it is recommended that three clinical trials be initiated during the first year of the BRMP program. The first two, in ovarian cancer and malignant lymphoma, addressing lack of confirmation of a positive formal trial. The third trial in renal cancer is itended to substantiate the claim, made in several anecdotal reports, that augmenting agents are effective in the treatment of that disease.

1. Confirmatory trial of BCG in ovarian cancer

Alberts and coworkers initially reported in 1977 and recently updated the results of a trial of BCG combined with chemotherapy in the treatment of ovarian cancer. In this study patients with disseminated ovarian carcinoma received adriamycin and cytoxan chemotherapy and were randomized to receive BCG immunotherapy 6 x 10^8 organisms by scarification to the four extremities, three times between cycles of chemotherapy. In the group receiving BCG there was a significant improvement in the response rate, the response duration and the survival compared to the group receiving chemotherapy alone.

Recommendation: It is recommended that at least one confirmatory trial of adriamycin plus cytoxan chemotherapy ± BCG immunotherapy be carried out in disseminated ovarian carcinoma. Patients should have not received prior chemotherapy, should have

histologically documented disseminated disease, should have measurable disease and should be available in large enough numbers to satisfy the statistical requirements for such a randomized phase 3 trial. These studies should be conducted by a qualified clinical group. This could be at either an individual institution or could be conducted by a Cooperative Group. (The Albert study was conducted by the Southwest Oncology Group.) The study should include immunological evaluation of the patients relevant to the biological therapy being administered. This aspect should be left to the individual investigators. However, it is recommended that an immunologist be part of the study team. The results of this confirmatory trial should be conclusive in determining whether or not BCG immunotherapy does indeed influence the remission rate, duration or survival in ovarian carcinoma and should be extremely important in influencing the future direction of the biological response modifier program.

2. Confirmatory trial of BCG in lymphoma

The rationale for application of immunomodulator agents includes their tropism for certain tissues and their probable effects on balance and feedback of lymphoid cell populations. Several clinical trials have suggested clinical benefit by nonspecific immunomodulators in various lymphoproliferative malignancies. These include the very large three arm trial of BCG added to chemotherapies for nonHodgkins lymphoma as carried out by the Southwest Oncology Group. The survival advantage of BCG in the adriamycin arm of induction (CHOP) merits confirmation. No difference has been apparent in the CR rate nor in remission duration.

It is recommended that a confirmatory trial be carried out with stage III and IV nodular poorly differentiated lymphoma. The chemotherapy induction will follow the CHOP arm of SWOG protocols 7426/-27 and 77/3/14. This regimen is:

Cyclophosphamide–750 mg/M^2 IV on day 1 only; hydroxyldaunomycin (adriamycin)–50 mg/M^2 IV on day 1 only; oncovin–1.4 mg/M^2 IV on day 1 (max. dose 2 mg/dose); prednisone–100 mg PO for 5 days.

This is repeated every 21 days for eight courses with careful restaging when response occurs. A second randomization of CR patients comparing maintenance of remission will be between BCG and no therapy. This phase 3 study should employ the BCG prepreparation, dose and schedule of the SWOG group study. It should include well chosen biologic response monitoring assays to attempt to identify subsets of better survival (or responding) patients.

Therapeutic Trial of BCG in patients with renal adenocarcinoma

Systemic chemotherapy is of marginal value in the treatment of metastatic renal adenocarcinoma; the beneficial effects attributed to chemotherapy are difficult to distinguish from the variations often encoutnered in the course of this disease. Progestational agents are the primary treatment for patients with metastic renal adenocarcinoma. Clinically useful remissions are unusual, however. True spontaneous partial or complete regression of cancer is a well recognized but rare event. However, renal adenocarcinoma is one of the tumor types for which spontaneous regression is most frequently reported. This suggests that the host immune system may modulate the growth of this tumor. A number of investigators have attempted immunotherapy in patients with metastatic renal adenocarcinoma.

Eidinger and Morales (Morales, A. and Eidinger, D., Bacillus Calmette-Guerin in the treatment of adenocarcinoma of the kidney. J. Urol. 115:377-380, 1976; Eidinger, D., Morales, A., BCG immunotherapy of metastatic adenocarcinoma of the kidney. Natl. Cancer Inst. Monog. 49:339-341, 1978) treated 10 patients with metastatic renal adenocarcinoma with BCG obtained from Institut Armand Frappier. Following a single intradermal innoculation, a 40 mg dose was administered weekly for 4 weeks, twice monthly for two months and then monthly using a multipuncture (Heaf Gun) apparatus. Four of 10 patients were reported to have responded objectively. Regression of pulmonary metastases was noted in 3 patients. In the fourth patient supraclavicular lymph node metastases regressed. Two of 4 patients had in addition to the single lesion other disease which remained stable. To date, 20 patients have been treated. The two two complete responders are disease free at 36 and 50 months (personal communication).

Several groups (Tykka, H., Hjelt, L., et al., Disappearance of lung metastases during immunotherapy in five patients suffering from renal carcinoma. Scand. J. Resp. Dis. Suppl. 89:123-134, 1974; Schapira, D.V., McCune, C.S., Henshaw, E.C., Treatment of advanced renal cell carcinoma with specific immunotherapy consisting of autologous tumor cells and C. parvum, Proc. Am. Soc. Clin. Oncol. 20:348, 1979; Neidhart, J.A., Murphy, S.G., et al., Active specific immunotherapy of Stage IV renal carcinoma with aggregated tumor antigen-adjuvant, Cancer, (submitted), have explored active specific immunotherapy. Eleven of 58 patients experienced objective tumor regression. These treatment techniques are more complicated than the use of BCG alone and are further limited by the need for autologous tumor tissue.

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