THE CANCER LETTER

1411 ALDENHAM LANE RESTON, VIRGINIA TELEPHONE 703-471-9695

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NINE SATURATION PROGRAM PLANNING WINNERS NAMED; NCI MAY REISSUE RFP LATER THIS YEAR

The first round of awards in NCI's community "saturation" program has been wrapped up with nine planning contracts of $100,000 each going to successful proposers who will "identify as far as possible the resources available in their communities, and organize and mobilize them to reduce morbidity and mortality from cancer."

The awards went to (the lead agency in each case is listed):

Connecticut State Dept. of Health; Research Corp. of the Univ. of Hawaii; Univ. of Pittsburgh; Community Cancer Control of Los Angeles; Univ. of Wisconsin Clinical Center; Rhode Island Dept. of Health; Fred Hutchinson Comprehensive Cancer Center is Seattle; Cancer Center of the Univ. of Rochester, N.Y.; and the Long Island Cancer

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In Brief

OMB STILL DRAGGING ITS FEET ON NEW CONSTRUCTION MONEY; SCHMIDT PRESSURE GETS 70 SLOTS FOR NCI

WORLD CONFERENCE on smoking and health June 2-5 in New York will include separate sessions on the relationship of smoking to cancer, pulmonary disease, and cardiovascular disease. E. Cuyler Hammond, Ernst Winder, and Gio Gori will chair the various cancer sessions; Wynder is also chairman of the general session on "Problems and Opportunities." The conference will be at the Waldorf Astoria. Contact Joseph Clark at ACS in New York or Robert Hadsell at NCI. . . . **"CANCER RATES AND RISKS,"** a paperback published by NCI's Biometry Branch, tells the incidence, risk factors, treatment and survival associated with cancer in the U.S. and the world. Single copies are available free from the NCI Office of Cancer Communications, Bethesda, Md. 20014. Bulk quantities may be ordered from USGPO, Washington, D.C. 20404 at $1.80 per copy. . . . **PERSONNEL FREEZE** that has threatened to create severe bottlenecks in the workflow at NCI was thawed slightly by an appeal by Benno Schmidt directly to President Ford. A letter from the chairman of the President's Cancer Panel to Ford was not acknowledged, but a few days later NCI got the word it would get 70 more positions, up from 1,118. It will mean a real gain of only 20-30, since NCI has been operating with about 45-50 more slots than authorized by the Office of Management & Budget and has been forced to leave positions unfilled that were opened by retirement and resignation. . . . **PIETRO GULLINO,** long-time NCI staff member, is the new chief of the Breast Cancer Task Force. . . . **OMB IS STILL** dragging its feet on releasing $9 million for new construction at UCLA, Salk Institute and New York Univ. NCI had been led to believe OMB would go along with those projects (***The Cancer Letter,*** April 25) without committing itself to other new construction, but the White House Budget office has not yet revealed which way it is going to go.

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COMMUNITY WORKSHOPS TO HELP BIDDERS ON NEW PLANNING RFP

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Council, Melville, N.Y.

Competition for the awards was intense, and unsuccessful proposers were bitterly disappointed in some cases. "We put an awful lot of work into this and stirred up a lot of people in our community. And for what?" commented a representative of one of the 24 agencies that lost out.

Their efforts may not have been in vain—they may get another shot at it. Larry Callan, associate director for community activities in the Div. of Cancer Control & Rehabilitation, said that a new round of RFPs in planning a community saturation program may be issued later this year.

If so, they will contain language spelling out with greater specificity what NCI meant by "community involvement," one of the key factors in rating the proposals in the first round. Most of the unsuccessful bidders failed to involve the broad range of organizations sought by NCI for the program.

Callan has offered to debrief the unsuccessful bidders, identify their soft areas and point out why they did not meet the criteria established for the program. He also hopes to set up planning workshops for community organizations during the summer.

Weaknesses in the unsuccessful proposals included:

- Failure to include obvious existing resources, such as Community Health Planning and Regional Medical Program repositories of medical facilities in the bidders' geographic areas.
- Failure to include information on clinical research in their communities.
- Ignoring epidemiological data available for the areas covered by the proposals.
- Failure to adequately define the "community" covered by the proposal.

The 18-month contracts call for the development of a five-year plan to involve community resources to attack the most serious cancer problems related to the social, economic and demographic characteristics of the community. The plan should be aimed at creating broad-based community support to transmit into practice what is known about the prevention and treatment of cancer and rehabilitation of cancer patients.

A tumor registry should be in operation by the end of the 18 months.

NCI will encourage the planning contract winners to go for the next round of implementation contract awards when their planning has been completed.

Announcement of the winners in the first round of implementation contracts is expected soon. Review of those applications has been completed, and NCI staff was scheduled to meet this week to select two or three for awards.

TRAINING OF SURGEONS MAY GET MORE SUPPORT FROM CANCER PROGRAM

NCI-supported clinical training programs should include more emphasis on the training of surgeons, Director Frank Rauscher, other NCI executives and members of the President's Cancer Panel agreed last week.

Rauscher told the Panel that he had heard members of the American Assn. for Cancer Research and American Society of Clinical Oncologists say at their San Diego meeting this month that NCI was not doing a good job in helping to train surgeons.

"Most cancers that are cured are cured by surgery, but it is the least supported modality, with practically no research on improving it," commented Panel member Lee Clark.

"I thought you surgeons feel you are about as good as you can get," Panel Chairman Benno Schmidt said.

"Some may feel that way, in their declining years," Clark answered.

Rauscher said that up to 90% of cancer surgery is being performed by general surgeons. NCI support of training radiotherapists and chemotherapists is helping to overcome shortages in those fields, "but we just are not training surgeons in oncology."

Clark said there is "still a crying need" for training pediatric cancer specialists. Vincent DeVita, director of the Div. of Cancer Treatment, pointed out that the pediatric specialists are better coordinated on a nationwide basis.

Thomas King, director of the Div. of Research Resources & Rehabilitation, noted that the Cancer Act gives NCI the option to develop special programs in clinical oncology, and surgery could be one. King said he hoped to present some program ideas to the National Cancer Advisory Board at its June meeting.

King said there is still a need for more medical oncologists, and that while the number of radiotherapists is increasing, they still need to be better dispersed around the country.

"To the question, should NCI be more aggressive and active in training surgeons, the answer is a qualified yes," Rauscher said.

Margaret Edwards, chief of DRR&C's Education Branch, reported on the status of NCI training programs in a memo to King. The memo follows:

"Presently there are 92 active clinical cancer training grants supported by $7.484 million earmarked in the fiscal year 1974 budget (all of these grants are forward-financed, i.e., money is awarded toward the end of one fiscal year and all grant periods begin on July 1 of the following fiscal year). Awards totalling $4 million are currently being made from fiscal year 1975 funds to 45 institutions with commitments extending through fiscal year 1976. There are 12 institutions which have commitments totalling $1.7 million which will require support from

fiscal year 1976 funds, extending through fiscal year 1977.

"A total of 62 applications for clinical cancer education grants have been reviewed in fiscal year 1975; 51 were acted on by the March Board and 11 will go to the June Board so they may be funded from the fiscal year 1975 allotment of $5 million. A total of $10 million was requested in those applications, and the recommended level of support (direct costs) totals $4.7 million.

"The 51 applications which went to the March Board came from 40 medicals schools (two schools of osteopathic medicine), seven dental schools, and four specialized hospitals. Applications from five medical schools (one a school of osteopathic medicine) were disapproved.

"The 11 applications which will be submitted to the June Board represent one school of public health, eight medical schools (two applications are supplemental requests from institutions whose applications were approved in March), one hospital and one dental school. Three applications from one medical school, the dental school, and the school of public health, were disapproved.

"Special permission was requested and obtain from Thomas Malone, chief of extramural research and training for NIH, to apply an 8% indirect cost rate to those grants rather than the higher negotiated rates used for research grants. This amount, added to the direct costs recommended by the committee, would bring the total requirements of 49 institutions (two with approved supplements) to $5 million.

"Both the clinical cancer training grants and the clinical cancer education grants are concerned with bringing about improvements in and expansion of cancer education at the undergraduate, graduate, and continuing education levels in those institutions with primary responsibility for training physicians and dentists. Stipends were provided for graduate trainees in certain clinical oncology specialties by the clinical cancer training grants, as well as for selected undergraduate medical and dental students during free (non-curricular) periods; no support was provided for residency training (exception: radiation therapy). The clinical cancer education grants provide support for selected undergraduate and graduate trainees classified as clinical assistants (undergraduate) and clinical associates (graduate).

"Since 1966 when the clinical cancer training program was initiated, more than 4,000 trainees were supported for periods of training extending up to three years in some individual instances in a variety of clinical specialties relative to cancer. Approximately one-half of these were undergraduate medical and dental students. A number of the directors of these broad-based, multidisciplinary training programs have become directors of or closely associated with cancer centers (Hammond, Durant, Shingleton, Owens, Huguley, Hartmann).

"The clinical cancer education grants are reviewed by the 25-member Clinical Cancer Education Committee, which also makes recommendations concerning manpower needs in clinical oncology."

Indirect costs for the clinical cancer education grants were held to 8% so that as many institutions as possible could be included in the program, which had a $5 million ceiling with fiscal 1975 funds. Schmidt said some institutions were "worried that this is a sign post that we will be cutting indirect support at a time when overhead costs are going up." Cutting payments for indirect costs "could turn a grant into a hardship," Schmidt commented.

The NIH average for indirect costs is 31.7%, King said.

The Panel agreed that cutting indirect cost payments in this instance was acceptable but should not establish a precedent.

REVIEW OF CENTER GRANTS TOUGHER, FUNDED LOWER THAN OTHERS, NCI SAYS

Research grant applications made through cancer centers receive "more stringent review" and are funded lower than traditional applications, John Yarbro, NCI associate director for cancer centers, said in a memo defending the centers program.

Yarbro insisted the tougher review applied to center grants is necessary because criticism of the centers program requires it and its review "to be like Caesar's wife."

Yarbro's memo was stimulated by an article in the newsletter, the *Blue Sheet*, which pointed out that 82% of approved center grants are funded compared with 60% for regular research grants. The memo follows:

"The most recent in a series of attacks upon the centers program relates to review. The issue here is to explain why the funding rate for cancer center grants is 82% as opposed to 60% for regular research grants and why the payline cutoffs for cancer center grants indicate a higher merit than traditional grants.

"The numbers reported in the *Blue Sheet* were as follows: Funding rate for cancer center grants 82% versus 60% for regular research grants. Priority score cutoffs for cancer center grants ranging from 245 to 270 with priority score cutoffs for traditional grants ranging between 284 to 291.

"An explanation for this phenomenon should comprise three elements:

"1. The first element is that center grants may contain multiple research projects, for example 20, whereas traditional grants normally contain only 1; if 10 of the component projects of a center grant are approved and 10 are disapproved the center grant may well be approved and funded; if the single project of a traditional grant is approved the grant will be funded, if it is disapproved the grant will not be funded; thus, if 20 research projects are proposed

as part of a center grant and 10 are disapproved the funding rate will show as 100% in terms of grants funded whereas if 20 research projects are requested as traditional grants and 10 are approved the funding rate will show at 50%. Conclusion: Funding rate is not a valid parameter for comparing center grants to traditional grants.

"2. The second element in the explanation of this phenomenon relates to the more pertinent parameter of comparison which is the dollar amounts applied for and the dollar amounts funded. For new center applications in FY 1975 requests were made for $79.4 million and $24 million were funded for a funding rate of 30.2% in terms of dollars applied for versus dollars awarded. For traditional grants $104.2 million were requested and $46.3 million were funded for a funding rate of 44.2% which compares dollars requested versus dollars awarded. Conclusion: The review of center grants is more stringent than the review of traditional grants as demonstrated by the fact that the funding rate based on dollars is considerably less for center grants.

"3. The third element in the explanation of the phenomenon is really in the form of a question: Why is it that the funding rate in center grants is lower than traditional grants and the priority scores of funded center grants show a cutoff line that is better than traditional grants? In answering this question we must depart from data and speculate, but I believe this speculation is on firm grounds. The most logical explanation for the more stringent review of center grants relates to the fact that all center grants are site visited and the programs are examined in detail on site. This inevitably results in a more stringent review. Conclusion: The more stringent review of center grants probably results from the fact that these grants are site visited.

"In summary then I believe that we can readily defend the review process in the cancer centers program on the basis of statistics with regard to dollars requested and dollars awarded and on the basis of the site visit which is a uniform practice in cancer center grant review.

"I can only say that in my judgment the quality of site visits for cancer center grants is superb, and I have been very much impressed with the critical nature of the reviews and with the quality of the site visit teams. In fact, the major criticism which I have heard of center grant site visits has been that the reviewers were too stringent in their cutbacks on requested levels of support, a charge that is supported to some extent by the numbers quoted above. I would defend such a practice, however, because the cancer centers program is a new program and is having a major impact across the country; as such, it can be expected to generate criticism from some groups who feel that it is not in their best interests for effective cancer centers to develop. For these reasons, then, it is necessary for the cancer centers program and the review of the program to be like Caesar's wife, more rigorous in the application of standards than the traditional programs."

In discussing Yarbro's memo, Ray Owen, member of the President's Cancer Panel, agreed that peer review is better when site visits are made. "You get better selection from a multiple application and help eliminate the weaker applications with site visits," Owen said.

Panel Chairman Benno Schmidt suggested that the weaker applicants "who can't compete with their colleagues at a cancer center" would have a better chance of being funded if they would leave the centers and submit their applications independently. "The bottom guy would be better off to go somewhere else," Schmidt said.

"We encourage them to try to go somewhere else," said Panel member Lee Clark, president of the Univ. of Texas System Cancer Center.

CYTOXAN ALONE, WITH ADRIAMYCIN SAID EFFECTIVE AGAINST BLADDER CANCER

A team of investigators at Roswell Park have reported significant results in clinical studies using cytoxan alone and cytoxan with adriamycin to treat transitional cell carcinoma of the bladder.

The team includes Claude Merrin, Ruben Cartagena, Zew Wajsman, George Baumgartner and Gerald Murphy.

In a paper presented at the annual meeting of the American Urological Assn. this month, the investigators reported on 49 patients who were entered in the study at Roswell Park from February, 1974, to April, 1975. A summary of the paper follows:

Traditionally, bladder cancer has been treated by a combination of surgery and/or radiotherapy. These modalities have been successful when the disease was localized to the bladder or the pelvis. In presence of generalized disease, failure has frequently been the case. In order to improve the prognosis of patients with potentially disseminated disease, a pilot study was developed to test the efficacy of cyclophosphamide (cytoxan) and adriamycin alone and in combination as adjuvant therapy to surgery.

All patients in the study had histologically proven transitional cell carcinoma of the bladder. All had objectively measurable lesions of malignant disease. The age of the patients ranged from 51 to 90 years old, with an average of 66.9 years. They were divided into three groups.

Group I consisted of 21 patients, 8 were Stage A, 7 were Stage B, one was Stage C and 5 were Stage D. They were treated with cytoxan 1 gm X m^2 (body surface area/bsa) every three weeks.

Group II consisted of 10 patients, 2 were Stage A, 1 was Stage B and 6 were Stage D. They were treated with adriamycin 75 mg/m^2 (bsa) every three weeks, up to a total dose of 500 mg.

Group III consisted of 18 patients, 7 were Stage A, 1 was Stage B and 10 were Stage D. They were treated with adriamycin 40 mg/m^2 (bsa) every three weeks plus cytoxan 200 mg/m^2 (bsa) every day for four days every three weeks starting on day 3.

In Group I (cytoxan), eight patients (38.1%) are presently in complete clinical remission. Of these patients, three are Stage A and five are Stage B. The period of remission has varied from eight to 12 months with an average of nine months. Three patients (14.2%) showed an objective response (1 Stage A, 1 Stage B and 1 Stage D). Three patients (14.2%) showed a subjective response (2 Stage A and 1 Stage C). Five patients (24%) remained stable (2 Stage A, 1 Stage B and 2 Stage D). Two patients (9.5%) progressed (1 Stage A and 1 Stage D).

In Group II (adriamycin) one patient (10%) is in complete clinical remission (Stage A) for 10 months. No other objective responses has been observed. One patient (10%) showed a subjective response (Stage B). Five patients (50%) remained stable (1 Stage A, 1 Stage C and 3 Stage D). Three patients (30%) progressed (3 Stage D).

In Group III (adriamycin and cytoxan) five patients (27.8%) are in complete clinical remission (3 Stage A and 2 Stage D), from four months to 14 months with an average of 10 months. Four patients (22.2%) showed an objective response (4 Stage D) and 7 patients (38.8%) remained stable (3 Stage A, 1 Stage B and 3 Stage D). Two patients (11.2%) progressed (2 Stage D). None of the patients in complete clinical remission in the three groups has had a clinical recurrence up to date.

The toxicity of the chemotherapy was manifested by various degrees of myelosuppression in the 49 patients treated. Transient GI upset manifested by nausea and vomiting was present in all the patients after administration of cytoxan. Ten patients had to be put on reverse isolation because of leukopenia, six patients required parenteral hyperalimentation because of mucositis and GI upset. No cardiac alterations were observed as a consequence of the administration of adriamycin. All the patients who received adriamycin developed transient alopecia.

In conclusion, chemotherapy of transitional cell carcinoma of the bladder with cytoxan alone and with cytoxan and adriamycin appears to be effective. Adriamycin seems to be less effective alone than combined with or compared to cytoxan. These studies suggest that these agents deserve further widespread use in the adjuvant chemotherapy of bladder cancer.

In the elaboration of this clinical study, we decided that cytoxan deserved to be evaluated and compared to adriamycin because it is excreted in the urine and has a definite toxic action in the bladder mucosa which has been well documented in patients on long term cytoxan therapy. Our results confirmed our theoretical considerations.

Contract Awards

NEW SUBCONTRACTS PLANNED IN BIOASSAY PROGRAM OPERATED BY TRACOR-JITCO

New subcontracts that will be awarded during the next 12 months under the bioassay prime contract held by Tracor-JITCO for the NCI carcinogenesis program probably will include inhalation studies. RFPs for that work and possibly for other bioassays of new chemicals will be issued later this year.

NCI is negotiating with Tracor-JITCO for renewal of the prime contract, which will expire May 30. The firm was awarded the contract in March, 1974, under which it assumed operational responsibility for 10 subcontracts in the bioassay program.

No new subcontract awards have been made during the first year of the prime contract program, but the firm and NCI are in the final review of proposals generated by RFP 74-5-10 (***The Cancer Letter,*** Jan. 24) involving long term carcinogenesis bioassay testing with rodents. It is possible that multiple awards will be made for those studies.

Meanwhile, NCI has stepped up its award of contracts with only five weeks left to the end of the fiscal year. Awards announced this week were:

Title: Viral studies in support of cancer chemotherapy patients
Contractor: Georgetown Univ., $181,285

Title: Preparation of bulk chemicals and drugs
Contractor: Parke, Davis, $293,122

Title: Preparation of bulk chemicals and drugs
Contractor: Pharm-Eco Laboratories, $206,259

Title: Award of additional effort and equipment for the basic research program at Frederick Cancer Research Center
Contractor: Litton Bionetics, $432,855

Title: Synthesis of CNS antitumor agents
Contractor: Northeastern Univ., $177,854

Title: Conduct immunological studies on breast carcinoma
Contractor: M.D. Anderson, $48,838

Title: Study and produce avian leukosis viruses
Contractor: Life Sciences, $418,825

Title: Conduct studies on the relationship of herpes simplex virus type 2 to urogenital cancer
Contractor: Univ. of California (Irvine), $96,610

Title: Maintenance of an irradiated monkey colony
Contractor: Emory Univ., $28,000

Title: Molecular studies of herpes type viruses of potential oncogenicity
Contractor: Univ. of North Carolina, $135,000

Title: Investigate the natural occurrence of RNA tumor viruses
Contractor: Jackson Laboratory, $31,750

Title: Studies of human milk and mammary tumors
Contractor: Institute for Medical Research, Camden, N.J., $450,000

Title: Study relationship between cells transformed by DNA and RNA tumor viruses
Contractor: Harvard College, $73,771

Title: Conduct studies of leukemia virus DNA polymerase
Contractor: MIT, $142,055

Title: Conduct a project for isolating type C virus from cultured leukemic cells
Contractor: Sidney Farber Cancer Center, $118,330

Title: Replication of oncogenic RNA viruses and its relation to human cancer
Contractor: Columbia Univ., $358,810

Title: Study molecular basis of viral carcinogenesis
Contractor: Albert Einstein College of Medicine, $410,000

Title: Hormonal control of gene expression in tumor viruses
Contractor: Univ. of California (San Francisco), $67,315

Title: Conduct Oncogenic studies of RNA tumor viruses
Contractor: UCLA, $64,397

ABSTRACTS OF OUTSTANDING PAPERS FROM AACR MEETING

The program committee for the 66th annual meeting of the American Assn. for Cancer Research singled out 29 papers as among the outstanding ones presented at the meeting. The following abstracts are from that list; 12 were published here last week, and the rest will appear in a subsequent issue of The Cancer Letter.

TRANSFORMATION OF CULTURED RAT ADRENOCORTICAL CELLS BY KIRSTEN MURINE SARCOMA VIRUS – *N. Auersperg, J.W. Jull, J.B. Hudson and E.J. Goddard, Cancer Research Centre, Univ. of British Columbia, Vancouver, B.C.*

This study demonstrates that Kirsten murine sarcoma virus (Ki-MSV) can transform differentiated epithelial cells. Cultures of normal adult rat adrenal cortex were exposed to Ki-MSV harvested from productive transformed NRK (normal rat kidney) cultures. Within a week, the adrenal cells, which are normally fusiform and aligned in parallel, became pleomorphic and piled up intensively. Saturation density increased from $5\text{-}10\times10^4$ to $5\text{-}10\times10^5$ cells/cm^2, population doubling time during exponential growth decreased from 36-40 to 16 hours, acid production increased and the growth rate became independent of a reduction in serum concentration from 10% to 1%. Inoculation of 2×10^6 cells into immunodepressed rats produced rapidly growing invasive tumors within 1 week. Histologically, the tumors were pleomorphic adrenocortical carcinomas with areas ranging from anaplasia to near-normal, highly differentiated adrenal tissue. In addition to histologic evidence of differentiation, metabolic studies using ^{14}C-pregnonolone showed that the transformed cells were capable of 20*a* hydroxylation and $\Delta 5,3\beta$ dehydrogenation, both characteristic of normal steroid-secreting tissues. The transformation of adrenocortical cells by Ki-MSV demonstrates the capacity of this agent to induce carcinomas in differentiated cells and widens the range of tissues known to be susceptible to MSV to include a secretory epithelium.

EFFECTS OF TETRAHYDROURIDINE (THU) ON THE UPTAKE AND METABOLISM OF ARABINOSYLCYTOSINE (ARA-C) BY HUMAN ACUTE MYELOGENOUS LEUKEMIA (AML) CELLS – *D.H.W. Ho, Carol K. Carter and Ti Li Loo, Univ. of Texas, M.D. Anderson Hospital & Tumor Institute*

Ara-C is clinically useful for treating AML. AML cells rapidly phosphorylate ara-C; however, they also show high deaminase (D) activity to inactivate ara-C. The effects of a D inhibitor, THU, on cellular levels of ara-C and its metabolites were studied in AML cells. After 30 min. pretreatment with or without THU (2×10^{-4} M) cells were incubated with ara-C-^{3}H (1 μg/ml) for 2 and 23 hrs. Intracellular ara-C and ara-U (aribinosyluracil) levels are negligible regardless of THU pretreatment. At 2 hr., 10% of intracellular nucleotides is derived from ara-U; however, at 23 hr. this is reduced to 5% if THU is present. At 2 hr. with or without THU, the ara-C nucleotides (0.8 μg) consist of ara-CMP (monophosphates) 11%; ara-CDP 21% and ara-CTP 68%. However, at 23 hr. without THU, 0.2 μg) of ara-C tides are found, 61% ara-CMP and 24% ara-CTP. But with THU, 0.8 μg of phosphorylated ara-C has been recovered with ara-CMP 32% and ara-CTP 53%. The incorporation of ara-C into acid insoluble fraction, though small, is significantly increased. Tissue levels of ara-CTP and its duration determine therapeutic efficacy of ara-C in experimental systems. Our findings of increasing intracellular ara-CTP by THU suggest the combination of ara-C with THU for the treatment of AML. Also, intracellular ara-CTP levels in vitro may predict clinical responses to ara-C.

MICROSOME-MEDIATED MUTAGENESIS IN CHINESE HAMSTER CELLS BY CHEMICAL ONCOGENS – *David F. Krahn and Charles Heidelberger, McArdle Lab., Univ. of Wisconsin*

In the presence of the 9000 x g supernatant fraction of rat-liver, NADPH and NADH, several chemical oncogens that require metabolic activation exhibited dose-dependent toxicity and produced an increase in the frequency of thio-guanine-resistant colonies in Chinese hamster V79 cells. Alone or in an incomplete system these chemicals were inactive. The LD_{50} values for aflatoxin B_1 (0.1 μg/ml), benzo[a]pyrene (4 μg/ml), and dimethylnitrosamine (1 mg/ml) were obtained with the use of liver homogenates obtained

from non-induced, methylcholanthrene-induced, and phenobarbital-induced rates, respectively. They also produced, respectively, 40, 160, and 30-fold increases in thioguanine-resistant variant colonies. Other oncogens studied were methylcholanthrene, β-naphthylamine, N-methyl-4-aminoazobenzene, and 2-acetylaminofluorene. Colonies surviving thioguanine at 15 μg/ml were isolated and characterized with respect to thioguanine and HAT resistance, HGPRT activity, and the stability of the phenotype during growth in the absence of thioguanine. These studies demonstrate that chemical oncogens requiring metabolic activation can be screened for mutagenic activity in cultured mammalian cell lines that are deficient in mixed-function oxidase activity.

STUDIES ON THE INACTIVATION OF GLUCOCORTICOID RECEPTORS – ***William B. Pratt, Carl J. Nielsen, and W. Mark Vogel, the Univ. of Michigan, Ann Arbor***

The purpose of this study is to determine if the inactivation of glucocorticoid receptors is the result of enzymic digestion or denaturation. Glucocorticoid receptors in cytosol preparations from various sources like the P1798 mouse lymphosarcoma (Kirkpatrick et al. J. Biol. Chem. *247*:70, 1972) and rat thymic lymphocytes (Bell and Munck, Biochem. J. *136*:97, 1973) are rapidly and irreversibly inactivated ($t^1/2$ at 37° ≈ 2 min.). The rate of inactivation of the L cell receptor is much slower. Under the same conditions at 0° the $t^1/2$ for inactivation of the L cell receptor is 32 hrs. vs. 2-5 hrs. for rat thymocytes. The receptor from thymocytes is markedly stabilized in the presence of both high and low affinity steroids. In contrast, the L cell receptor (which is also stabilized by the high affinity steroid, triamcinolone acetonide) is inactivated more rapidly in the presence of weaker ligands like cortisol and dexamethasone. If the 100,000g supernatant of L cells is mixed with the 27,000g supernatant of thymocytes, the L cell receptor is inactivated at the same rapid rate as that of thymocytes. Heating the thymocyte preparation to 90° inactivates its ability to degrade the L cell receptor. This observation and other data to be presented suggest that the rapid inactivation of the glucocorticoid receptor in thymocytes is due to degrading enzyme(s) that might be able to be separated from the receptor.

IDENTIFICATION OF CHICK THYMIDINE KINASE (TK) DETERMINANT IN SOMATIC CELL HYBRIDS OF CHICK ERYTHROCYTES AND TK-DEFICIENT MOUSE CELLS – ***W.-C. leung, T.R. Chen, D.R. Dubbs, and S. Kit, Div. of Biochemical Virology, Baylor College of Medicine, and Graduate School of Biomedical Sciences, Univ. of Texas***

Introduction of a chick erythrocyte nucleus into the cytoplasm of TK-deficient mouse [LM(TK⁻)] cells results in the activation of chick DNA synthesis. Somatic cell hybrids obtained from the heterokaryons by HATG selection contain reactivated chick cytosol TK-F and mouse mitochondrial TK-A, but not mouse TK-F or chick TK-A activities, as demonstrated by disc PAGE and electrofocusing analyses. The reactivation processes are models for events which may occur when quiescent normal cells are transformed to neoplasia. We have now demonstrated that the chick-mouse hybrids contain chick chromosomes. Karyotypes were analyzed by the method which sequentially reveals Q- and C-bands. Four hybrid clones contained the full complement of mouse chromosomes and 1-3 chick micro-chromosomes. Counterselection of the hybrids in BrUdR medium resulted in the loss of chick cytosol TK-F activity and the acrocentric chick chromosome, which stained weakly with quinacrine mustard, but mouse mitochondrial TK-A was unaffected. These BrUdR-resistant clones could not grow in HATG medium. Consequently, we have demonstrated that (1) the chick cytosol TK gene is on a member of the micro-chromosomes and (2) selection in HATG and BrUdR-containing medium involves only cytosol TK-F.

LEUKOCYTIC DIFFERENTIATION IN FRIEND LEUKEMIA INDUCED BY COLONY-STIMULATING ACTIVITY – ***David W. Golde, Annick Faille, Ann Sullivan, and Charlotte Friend, UCLA School of Medicine and Mt. Sinai School of Medicine, New York***

The Friend leukemic cell is thought to be an erythroid precursor because established lines have the capacity for erythroid differentiation. We found that cultured spleen cells of mice with terminal Friend virus-induced leukemia differentiated into granulocytes and monocytes in the presence of colony-stimulating activity (CSA). Leukemic DBA/2 mice were sacrificed about 1 day before anticipated death. Normal DBA/2 cells served as controls and gravid mouse uterus extract was the source of CSA. Spleen cells were cultured in agar for assay of granulocyte-monocyte colony-forming cells (CFC) and in liquid suspension (Marbrook chamber). No growth occured in agar without CSA. When CSA was added, cloning efficiency was 10 times control and the colonies contained normally differentiated leukocytes. Total CFC per leukemic spleen was 350 times normal. Cells did not survive in liquid culture without CSA. CSA caused an increase in ^{3}H-thymidine labeling indices and cell numbers.

Generation of CFC in suspension cultures was also dependent on CSA which stimulated an 8-fold increase in CFC per culture at 7 days. These data indicate that leukemic spleens contain increased numbers of stem cells with the capacity to respond to CSA and differentiate into mature granulocytes and monocytes in vitro.

RECOGNITION OF THE HUMAN HEMOPOIETIC STEM CELL – ***Ronald D. Barr, Jacqueline Whang-Peng, and Seymour M. Perry, NIH***

The monophyletic theory of hemopoiesis demands the existence of a single cell capable of differentiation

into all the formed elements of the blood. Such an entity has to date escaped definitive morphological identification in man, and this study was therefore undertaken in an effort to recognize the human stem cell.

Peripheral blood was separated by Ficoll-Hypaque density sedimentation and the "mononuclears" harvested and subjected to E-rosetting. The residual cells were applied to a sucrose gradient and separated by velocity sedientation at unit gravity. Two fractions were thereby obtained—of of pure, small lymphocytes (non-T) and the other a monocyte concentrate (85% monocytes, 10% basophils, 5% lymphocytes). On individual culture of these fractions within diffusion chambers implanted intraperitoneally in lethally irradiated mice, only the monocyte concentrate evidenced cellular transformation and differentiation, consistently producing macrophages, granulocyte precursors and megakaryocytes and, on occasion, normoblasts. "Mononuclears" were also subjected to EAC´rosetting and the residual pure lymphocyte preparation likewise showed stem cell activity on culture.

The hemopoietic stem cells were thus identified as a small, morphologically homogeneous subpopulation of lymphocytes, separable from the peripheral blood leukocyte mass on the basis of rosetting characteristics and large cell volume.

THE POSSIBLE ROLE OF LAF AS A PHYSIOLOGICAL MEDIATOR IN THE IMMUNE RESPONSE – ***Gershwin T. Blyden and Robert E. Handschumacher, Yale Univ. School of Medicine***

Lymphocyte activating factor (LAF) is possibly a physiological mitogen for thymus and T cells (Gery and Waksman). Reports from this laboratory outlined the preliminary purification and characterization of this peptide. In addition to adherent cells from mice and human blood, LAF is produced by cells from many species such as guinea pig macrophages, dog leukocytes, spleen and lung macrophages and monkey leukocytes. However, under similar conditions, activity was not produced by cultures of L1210, L5178Y, vero, BHK, HeLa or L-fibroblasts. An autogenic response could be demonstrated with LAF produced from a Rhesus monkey using thymocytes or cells from the spleen or lymph nodes of the same animal.

The response evoked by partially purified LAF on thymocyte cultures is enhanced by mercaptoethanol and brings up to 10$ of mouse thymocytes into mitosis. LAF activity is not affected by the sulfhydryl reagent iodoacetate or the esterase inhibitor phenylmethylsulfonyl fluoride (10^{-4}M. A selectivity of action within the cell population of the thymus was demonstrated by a peak response in animals completing thymic maturation (8 weeks) and the response is resistant to cortisone. Enhanced target cell response was seen in mature mice (18 weeks) bearing the tumor suggesting a relationship of the response t creased demands for cellular immunity.

HAMSTER MELANOCYTE CONTACT-INHIBITORY FACTOR (MCIF): EFFECTS TRANSCEND TISSUE AND SPECIES BARRIERS – ***George Lipkin and Margaret E. Knecht, Dept. of Dermatology, NYU School of Medicine***

A previous report described the isolation, from culturesof contact-inhibited hamster melanocytes, of a high molecular weight protein which restores contact inhibition of growth to hamster malignant melanocytes (PNAS *71*:849-853, 1974). The present study examined tissue and species specificities of this effect. MCIF was identified on analytic polyacrylamide gels and isolated on Sephadex G_{200}, and its effects upon growth and morphology of neoplastic cell lines were studied in a micro-well system. Cell types included mouse B16 melanoma, rat glioma, neurinoma, and neuroblastoma, and human melanomas (4) and colon carcinomas (2). MCIF produced identical changes of flatness, orientation, and fibroblast-like morphology in mouse and human melanomas as described earlier in hamster melanoma cultures. It significantly reduced saturation densities of cultures of all cell types studied (41-86%) with no loss of viability. On the basis of estimated molecular weight ($>$180000) and kinetics of inhibition of mitosis, MCIF differs both from cAMP and chalone. It promotes stable cell contacts leading to inhibition of growth, and its effects transcend some tissue and species barriers. MCIF is the first cell protein identified which restores contact inhibition of growth to malignant cell types, and may be the prototype for a critical class of surface-associated proteins concerned with regulation of normal cell-cell interactions.

SOLE SOURCE NEGOTIATIONS

Proposals listed here are for information purposes only. RFPs are not available.

Title: Study of high risk breast cancer families
Contractor: Michigan Cancer Foundation

Title: Technical writing services in support of cancer related public inquiries
Contractor: Biospherics Inc.

Title: Optimizing electrophoretic separation of proteins with new hydrogels
Contractor: Polysciences Inc., Warrington, Pa.

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