NATIONAL CANCER INSTITUTE

ANNUAL REPORT

October 1, 1983 through September 30, 1984

CONTENTS

ANNUAL REPORT

DIVISION OF CANCER TREATMENT

October 1, 1983 through September 30, 1984

The Division of Cancer Treatment (DCT) is responsible for the development, implementation, and evaluation of cancer treatment. Research is supported in surgical oncology, radiotherapy, immunotherapy, and chemotherapy both alone and in combination. The DCT coordinates both extramural and intramural initiatives. Investigator initiated laboratory and clinical research is supported by research grants, while more focused activities (such as specific treatment development) are funded through either contracts or cooperative agreements. Intramural laboratory and clinical programs complement the extramural activities of the Division.

Personnel and Organization

The Division is operationally divided into five programs, each headed by an Associate Director. A current organizational chart is shown in Figure 1, and reflects changes which occurred during the past year. The Low Level Radiation Effects Branch was transferred to the Division of Cancer Etiology. The Scientific Information Branch was transferred to the Office of the Director, National Cancer Institute. In addition, there were several changes in personnel:

A. Office of the Director (OD)

- Dr. Gregory Curt transferred from the Clinical Oncology Program to serve as Special Assistant for Clinical Affairs, to the Director, DCT.
- Dr. Saul Schepartz left the DCT to assume a position as Associate Vice President for Academic/Industrial Relationships at the University of Medicine and Dentistry of New Jersey.
- Dr. Arnold Welch, a Cancer Expert in the Drug Evaluation Branch, has been temporarily appointed as Acting Deputy Director.
- Mr. Michael Goldrich left the Division Administrative Officer position to assume the Executive Officer position in the National Institute of Allergy and Infectious Diseases.
- Mr. Donald Christoferson, former Deputy Administrative Officer, has been appointed Administrative Officer.

B. Radiation Research Program (RRP)

- Dr. David Pistenmaa left the DCT Associate Directorship of RRP to enter private practice at Fairfax Hospital, Fairfax, Virginia.
- Dr. Francis Mahoney has been functioning as Acting Associate Director.

- Dr. Francis Ruzicka joined the staff as Chief, Diagnostic Imaging Research Branch.

- The Low Level Radiation Effects Branch was transferred to the Division of Cancer Etiology.

C. Cancer Therapy Evaluation Program (CTEP)

- Dr. Michael Friedman was appointed Chief, Clinical Investigations Branch.

D. Developmental Therapeutics Program (DTP)

- Dr. Michael Boyd, former Chief, Laboratory of Experimental Therapeutics and Metabolism was appointed Associate Director.

- Dr. Hildegard Schuller was appointed Acting Chief, Laboratory of Experimental Therapeutics and Metabolism.

E. Biological Response Modifiers Program (BRMP)

- Dr. Robert Oldham, former Associate Director, left the DCT to enter private industry.

- Dr. Ronald Herberman was appointed as Acting Associate Director.

- Dr. Cedric Long was appointed Acting Branch Chief, Biological Resources Branch.

PROGRAM HIGHLIGHTS

Program area accomplishments will be detailed in individual annual reports. The following summaries describe selected activities within each program during Fiscal Year 1984.

Office of the Director

International Treatment Research

International treatment research activities of the Division are coordinated through the Office of the Director. Upon Dr. Schepartz' departure, the Japanese-American Bilateral Agreement was administered by Dr. Michael Friedman, while the Division's Bilateral Agreements with France, Italy, Federal Republic of Germany, People's Republic of China, Egypt, and Poland were administered by Dr. Gregory Curt. These Bilateral Agreements foster the international exchange of scientists which is critical to the dissemination of the rapidly-expanding and optimally shared data base of cancer treatment research. In addition, the Division maintains liaison offices at the Japanese Foundation for Cancer Research in Tokyo and the Institute Jules Bordet in Brussels. These programs in particular have led to valuable exchanges of new drugs and developing rationales of new treatment protocols with enhancement of clinical research in this country and abroad.

The most active areas of dialog we have included the treatment program of the U.S.-Japan Agreement which has continued to concentrate on problems of therapy with drugs and biological response modifiers, as well as research in radiotherapy with special emphasis on newly available heavy particle treatment. Two workshops were held under the auspices of the Agreement during the past year, one on the central problem of drug resistance in cancer and rationales for preventing or reversing this phenomenon and a second program review meeting that concentrated on the development of drugs and biological response modifiers.

In addition to supporting the exchange of scientific personnel, the Italian-American Bilateral Agreement underscored areas of collaborative research with a workshop in Bethesda which concentrated on "Diagnostic and Therapeutic Use of Monoclonal Antibodies" as well as "Mechanisms of Tumor Cell Metastasis and Effects of Drugs." Through collaborative initiatives with Istituto Nazionale per lo Studio E La Cura Dei Tumori, the DCT has pioneered a major effort in breast cancer. This work has dealt primarily with adjuvant therapy of resectable disease, and the results have received world-wide attention.

During the past year, the French-American Bilateral Agreement has sponsored the exchange of many young scientists interested in treatment-related research. A particularly important workshop was held in Bethesda under the framework of the Agreement dealing with "The Role of Bone Marrow Transplantation in Hematologic Malignancy."

Cooperative relationships with European cancer researchers have been strengthened by the Division's relationship with the Institute Jules Bordet in Brussels, Belgium. This interaction has both preclinical and clinical components. In order to identify new agents which may be useful in the treatment of cancer, drugs collected in Northern Europe and the United States are screened at the Institute Jules Bordet against in vivo animal tumors in accordance with established NCI protocols. Testing is currently being conducted at a level of approximately 11,000 L1210 test equivalents per year. In addition, important clinical programs are sponsored by the agreement. Through its "Cancer Chemotherapy Research Collaborative Office" at the Institut Jules Bordet in Brussels, Belgium, DCT maintains interaction with investigators of European nations concerning ongoing cancer research programs on both continents. The Brussels office has been especially useful in the areas of experimental and clinical pharmacology, clinical trials, and the organization of symposia jointly conducted by American and European investigators. It relates closely to the European pharmaceutical industry, providing a flow of new agents with potential anticancer activity. Fifty compounds are now in various stages of clinical development.

The Pan American Health Organization conducts collaborative treatment research with the best U.S. and Latin American investigators. The Group's new administrative format, which focuses on the best collaborating institutions, is working well. Recently, two Phase II studies of gastric cancer have been completed and two additional Phase II trials (isophosphamide, 4'epiadriamycin) are planned in this disease. In addition, an important

randomized trial compared relative activity and toxicity of two platinum analogs (CBDCA and CHIPS) is planned for patients with previously untreated cervical carcinoma.

Finally, personnel of DCT play key roles in the NCI Bilateral Agreements with China, Egypt, Federal Republic of Germany, and the USSR through participation in: clinical trials, the evaluation of activity of substances indicating properties for biologic response modification, and programs in experimental/development therapeutics.

SCIENTIFIC PROGRAMS

The mission of the DCT in discovering and implementing improved cancer therapy is pursued through extramural and intramural research encompassing drug development, radiation therapy, surgery, and biological agents. Highlights of preclinical and clinical research accomplishments during the past year are summarized here.

Surgical Oncology

Surgery plays a central role in cancer treatment; of the 800,000 patients who are annually diagnosed as having cancer, surgery is the primary form of therapy in over 400,000, and half of these patients will be cured and need no further treatment. Looking at the data from a different perspective, of the 350,000 patients who are annually cured of cancer, 60% are cured by surgery, 25% by radiotherapy and 15% by chemotherapy, either alone or in combination with other modalities. Recognizing the importance of the surgeon in the treatment of cancer patients, the Office of the Director organized the National Institutes of Health's participation in the 1984 meeting of the Society of Surgical Oncology to acquaint surgeons with the current initiatives by DCT towards support of surgical oncology as a subspecialty. These are detailed in the annual report of the Cancer Therapy Evaluation Program. In addition, Dr. Chabner served on the Commission of Cancer of the American College of Surgeons, delivering the keynote address of the College's annual meeting on "The National Cancer Institute and its relation to the American College of Surgeons."

Intramural Research Accomplishments

The identification of HTLV-III as the putative etiologic agent of Acquired Immunodeficiency Syndrome (AIDS) by scientists in the Laboratory of Tumor Cell Biology of the Developmental Therapeutics Program represents an important scientific breakthrough. This discovery has permitted the immediate development of an effective transfusion screening test to protect the nation's blood supply. In addition, identification of HTLV-III will allow eventual development of an effective vaccine for high risk individuals. Finally, this discovery will advance our basic understanding of cancer as it relates to the host immune system.

Researchers at the NCI-Navy Medical Oncology Branch discovered specific oncogene amplification in human lung cancer cell lines. This amplification results in increased tumor growth, cloning efficiency, and radiation resistance, suggesting that the amplification of oncogenes and their products may have important biologic and clinical implications.

Other intramural research accomplishments include a randomized trial demonstrating both effectiveness and improved cosmesis of breast-sparing surgery in combination with definitive radiation in treating early stage breast cancer. This trial provides a rationale to improve the quality of life of patients with a common malignancy without jeopardizing survival. Importantly, this trial included dosimetry studies to quantitate radiation doses to the opposite breast to assess risk of development of a second primary tumor. New combination chemotherapy regimens for poor prognosis testicular cancer and advanced diffuse aggressive lymphomas have doubled the previously reported disease-free survival rates. Combination chemotherapy and radiotherapy in patients with limited stage small cell lung cancer have resulted in the best survival (33%) ever reported at 5 years.

In addition, intramural researchers have demonstrated the efficacy of high dose methotrexate as an alternative to intrathecal drug plus radiation in CNS prophylaxis in children with acute leukemia. The efficacy of this treatment appears superior to currently available approaches. Randomized clinical studies have demonstrated that limb-sparing surgery in combination with local radiation or systemic chemotherapy is equivalent to amputation in patients with soft tissue sarcoma. Patients can thus be spared the disability of radical surgical treatment. High dose cisplatinum has been safely administered to patients with ovarian cancer with high response rates. By understanding the mechanism of drug activation, nephrotoxicity has been virtually eliminated as a toxic drug effect. Combination chemo-hormonal therapy has achieved a 95% overall response rate in patients with unoperable Stage III or inflammatory breast cancer, offering a new approach to previously suboptimal treatment of these diseases.

The intramural BRMP has demonstrated the efficacy of recombinant alpha interferon for favorable histology, non-Hodgkin's lymphoma and cutaneous T-cell lymphoma. Imaging trials with T-cell and melanoma specific antibodies have demonstrated excellent tumor localization.

PRECLINICAL RESEARCH ACCOMPLISHMENTS

Drug Development

Consistent with the move toward more rational drug use in the clinics, the process of drug discovery at DCT has recently changed as outlined in Table 1. The most important have been two new innovations in screening that are based on the idea that solid tumors, and particularly those of human origin, may be more appropriate models for selection of drugs for trial in man. To test this hypothesis, the DCT set up a panel of mouse and human solid tumors to supplement the mouse leukemia model in previous use. A second experimental screen utilizes human tumors grown in culture to determine the activity of candidate compounds. Both new screens have recognized potentially useful drugs in man that are undergoing clinical development.

TABLE 1

NEW APPROACHES TO DRUG DEVELOPMENT

1. New screening system:

   Human tumor colony-forming assay
   Tumor panel
   Antimetastatic screen
   Differentiation screen

2. Expedited clinical trial:

   New toxicology protocol
   Dose escalation based on drug levels in blood
   Cooperation with industry

3. New sources of compounds:

   National drug discovery groups
   Industry

In order to develop treatment strategies and new and potentially better chemotherapeutic agents for the treatment of metastases, laboratory models of metastatic cancer have been developed. Recent studies have demonstrated that it is possible to grow human tumors in nude (athymic) mice, while preserving or even enhancing their metastatic properties. Evaluation of these models at the Frederick Cancer Research Facility is directed toward assessments of their use for new anticancer drug discovery.

New screening systems have been developed to discover novel anticancer drugs with the ability to induce tumor cell differentiation. Thus, mouse erythroleukemia cells can be induced to differentiate in the presence of hexamethylene bisacetamide (HMBA). These cells lose the ability to proliferate, and become capable of producing hemoglobin characteristic of mature erthyrocytes. Similarly, HL-60 human promyelocytic leukemia cells isolated from a patient have been induced to differentiate into cells that have many of the morphological features of mature granulocytes by exposure to a wide variety of agents, including HMBA, retinoic acids, 3-deazauridine, and others. Discovery of "differentiating agents" indicates the potential for exploiting a new approach to cancer treatment, in addition to classical chemotherapy (which depends on cell kill), immunotherapy, radiation, and surgery. HMBA, the most potent inducer of its chemical class, is rapidly being developed to clinical trials that are expected to begin within a year.

At the level of the clinic, progress has been made in simplifying and improving the safety of new drug trials. A new NCI toxicology protocol in which starting doses are based on mouse lethality studies and been subsequently confirmed to a limited extent in dogs has thus far yielded safe starting doses in all phase I trials in the past two years. The

UCT has instituted a study to determine the value of using drug concentrations in blood as a guide for dose escalation in phase I trial; this study is an outgrowth of an appreciation that in the usual phase I trial a median of seven escalations of dose are required to reach maximally tolerated doses. Thus, most patients in these trials are treated at suboptimal dose levels and have little chance of responding. Our hypothesis is that the drug levels in blood associated with dose-limiting toxicity in mice can be used as a target for dose escalation in man. We expect that in the next decade clinical monitoring of drug levels in blood will allow greater individualization of therapy and compensation for problems such as variable bioavailability, altered drug elimination, or dose adjustment for organ dysfunction.

Biological Response Modifiers Studies

Preclinical treatment research in biological response modifiers has focused on the potential of immunomodulating agents, interferons, cytokines, lymphokines, monoclonal antibodies, and oncogene inactivation as useful cancer treatment strategies. The Preclinical Screening Laboratory of the BRMP has identified immunomodulating agents which retard the development of carcinogen-induced tumors in mice and rats and are capable of inhibiting the growth and spread of transplantable tumors. A major focus of research in the BRMP involves the role of natural effector cells in resistance against cancer. There have been extensive studies on natural killer (NK) cells. Interferons are a family of proteins with antiviral, antiproliferative, and antitumor activity that have also been shown to have potent effects on the cellular immune system, particularly on natural killer cells and macrophages. Interferons also appear to be important for mediating host resistance against tumor growth.

An increasing number of monoclonal antibodies are now becoming available with a high degree of specificity for a variety of human tumors including melanoma, colon carcinoma, neuroblastoma, lymphoma, and lung cancer. Techniques have been developed to conjugate these antibodies to toxins, cytolytic drugs, and radioisotopes. *In vitro* and *in vivo* studies have demonstrated considerable promise for selective antitumor effects by such monoclonal antibody-toxin conjugates. The specificity of the immunoconjugates for tumor cells appears to be several logs higher than for normal body tissues; thus these conjugates have the advantage of a high degree of tumor specificity and low systemic toxicity.

Preclinical Radiation Research

Radiobiology research has focused on the study of basic interactions of radiation with biological systems, the effects of dose fractionation, the interaction with chemotherapeutic agents, and the usefulness of predictive assays of radiosensitivity. In addition, new radiation sensitizers and protectors are being developed through a better understanding of the relationship between molecular structure and radiobiological activity.

CLINICAL RESEARCH ACCOMPLISHMENTS

Drug Development

Important studies in drug development have been completed during the past year. Phase II trials have confirmed the activity of mitoxantrone and bisantrine in breast cancer. Mitoxantrone is also active in leukemias, lymphomas and hepatoma. AZQ has reproducible activity in primary and secondary brain tumors as well as in lymphomas. Dichloromethotrexate has substantial activity in carcinomas of the bladder, cervix, and head and neck.

Important phase III studies have been completed during the past year. Several Several groups have reported responses to low-dose cytarabine therapy in patients with preleukemic myelodysplastic syndromes. This approach has been based on the demonstration of cytarabine as a differentiation agent in vitro. Clinical responses have been reported in 11 of 21 patients treated with intermittent subcutaneous low-dose cytarabine, and 8 of 8 patients treated with 7- to 21-day low-dose continuous infusion cytarabine. These early data suggest that exploitation of the differentiating ability of certain agents may provide a relatively less toxic but effective approach to treating these disorders, which usually occur in the elderly and often debilitated patients.

Based on preliminary encouraging results in pilot studies, a large intergroup cooperative trial was organized to determine the potential of LHRH agonists ± antiandrogens in the treatment of metastatic prostate cancer. This randomized trial will determine if new approaches to endocrine ablation offer a significant advantage to systemic estrogens or surgical castration and demonstrate that the cooperative groups offer a unique resource to answer important clinical questions efficiently and definitively.

Biological Response Modifiers

Alpha interferon has been established to have reproducible activity in Kaposi's sarcoma associated with acquired immunodeficiency syndrome (AIDS). In four separate clinical trials, both natural and recombinant preparations have resulted in a 30-40% response rate. In addition, published results have confirmed activity of interferon in renal cell cancer, hairy cell leukemia, chronic myelogenous leukemia, and nodular lymphoma. Early results from the Gynecologic Oncology Group have demonstrated the activity of interferon in a pilot study of ovarian cancer as well.

Under the conditions of cytoreductive therapy, both MEV2 and poly-ICLC have been found to cause an earlier reconstitution of bone marrow cellularity as well as effector cell responses.

Radiation Research

Intraoperative radiotherapy is undergoing evaluation as a treatment for intra abdominal malignancies. This approach alone or in combination with a radiosensitizer, promises improved control of localized malignancy. Phototherapy, the use of light to activate hematophorphyrin derivatives, has demonstrated that many tumor types which are non-responsive to

other modalities may respond to this modality. Of particular interest, bronchogeneic tumors have responded dramatically with a large number of complete responses being recorded. Newer radiation sensitizers hold promise for improved therapeutic index. Encouraging preliminary results are being reported on the use of neutron therapy of malignant glioma, prostatic carcinoma, and bladder cancer.

In summary, half of the patients diagnosed with cancer this year will likely be cured of their disease by current therapies, and the National Cancer Institute is committed further to reduce cancer mortality by 50% of today's rate by the year 2000. Improvements in cancer patient survival can be anticipated as new therapies are discovered and more standard treatments are used more effectively.

Publications

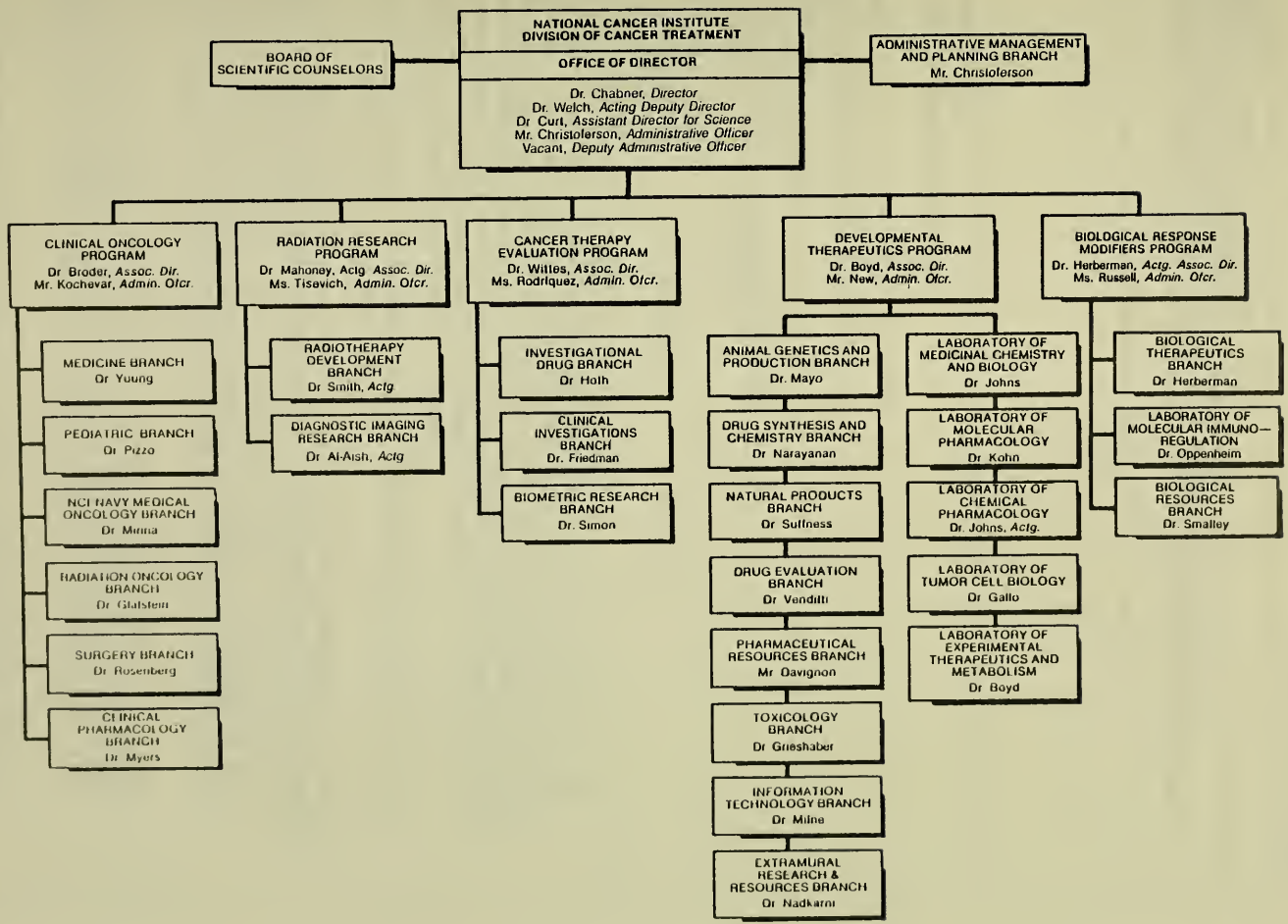
Chabner, B.A. and Schepartz, S.A.: Future directions for anticancer drug development. Monograph: Proc. of Cancer 1981/Cancer 2001--An International Colloquium (M.D. Anderson). (In Press)

Chabner, B.A. and Curt, G.A.: Editorial: Surgical oncology research development: The perspective of the National Cancer Institute. Cancer Treat. Rep., 68: 825-829, 1984.

Chabner, B.A. et al. Cancer Chemotherapy: Progress and Expectations. Cancer. (In Press)

Figure I

NATIONAL CANCER INSTITUTE, DIVISION OF CANCER TREATMENT
JUNE 1, 1984



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07101-09 DSCB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Computer Methods for Drug Preselection Based on Structure-Activity

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Louis Hodes, Acquisition Section, DS&CB, DTP, DCT, NCI, NIH

COOPERATING UNITS *(if any)*
Chemical Abstracts Service

LAB/BRANCH
Drug Synthesis & Chemistry Branch

SECTION
Acquisition Section

INSTITUTE AND LOCATION
NCI, NIH, Silver Spring, Maryland 20910

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Molecular fragment statistics from compounds tested in the prescreen, P388 leukemia, have been used to create programs that provide estimates of antitumor activity and novelty. For the past five years, these estimates have aided the medicinal chemist in selecting compounds for screening. In selecting our current input of 10,000 compounds per year, two to three times that many potential acquisitions are run through the programs. Refinements and extensions are continuously being introduced.

This year data from L1210 leukemia and B16 melanoma were combined with P388 into an aggregate antitumor model.

Also, a large-scale literature surveillance project was undertaken by running several hundred thousand compounds through the antitumor activity and novelty programs. These compounds were registered by Chemical Abstracts Service (CAS) before 1978 when DTP began its own literature searches. In contrast to the acquisition stream, where every structure is considered, only the top 5% according to an optimized activity and novelty criterion are examined as candidates to be requested for acquisition.

This year also wrought the conversion from CAS to DCRT as part of the new Drug Information System. This change was accompanied by a switch from the atom-centered fragments used in the Inquiry system to the more efficiently generated bond-centered fragments originally designed for literature surveillance.

As an experiment in combining physical parameters with structure features, the whole set of data was separated according to disjoint ranges of log P, the octanol/water partition coefficient.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 03584-12 PRB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Research in the Development of Dosage Forms of New Antitumor Drugs

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	James C. Cradock	Head	A&PDS	PRB	NCI
Other:	Karl P. Flora	Chemist	A&PDS	PRB	NCI
	Babu R. Vishnuvajjala	Visiting Assoc.	A&PDS	PRB	NCI
	Yuen Cheung	Visiting Fellow	A&PDS	PRB	NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Pharmaceutical Resources Branch

SECTION
Analytical and Product Development Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.4	2.4	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project describes the activities of the formulation laboratory of the Pharmaceutical Resources Branch. These studies are directed toward resolving problems inherent in the intravenous delivery of antitumor agents and relate primarily to problems of inadequate water solubility and stability. Liposomes are being studied to assess their suitability to improve the stability of several poorly water soluble and unstable compounds (Spiromustine, NSC 278214, etc.)

A stability indicating HPLC assay has been developed for the simultaneous determination of three intrathecal drugs: methotrexate, cytarabine and hydrocortisone sodium succinate. The stability of these agents has been evaluated in four common pharmaceutical vehicles.

Several water soluble prodrugs of camptothecin have been prepared. The N,N-diethylglycine derivative was synthesized using naturally occurring camptothecin as the starting material. Antitumor data indicate activity and potency equivalent to results obtained with camptothecin.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06142-07 LCHPH

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Relationships Between In Vitro and In Vivo Drug Antitumor Action

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Daniel S. Zaharko	Pharmacologist	LCP, NCI
Others:	Joseph M. Covey	Staff Fellow	LCP, NCI
	Conception Muneses	Chemist	LCP, NCI
	Ernestine Gregory	Biologist	LCP, NCI

COOPERATING UNITS *(if any)*
Laboratory of Molecular Pharmacology, Division of Cancer Treatment, NCI; Laboratory of Medicinal Chemical & Biology, Division of Cancer Treatment, NCI; Department of Nuclear Medicine, Clinical Center

LAB/BRANCH
Laboratory of Chemical Pharmacology

SECTION
Drug Kinetics and Therapeutics

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland, 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.2	1.4	1.8

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of these experiments is to give a better understanding of the mode of action of selected antitumor agents by conducting in vitro and in vivo studies with mouse tumor systems. L1210 leukemia was used to measure drug effects. Investigations are being conducted with 5-aza-2'-deoxycytidine (DAC), dihydro-5-azacytidine (DHAC) and the arabinoside analogue of 5-azacytidine (ARA-AC). The refractory nature of a few L1210 cells to treatment with the most potent of these three compounds, DAC, become apparent during these investigations. Even though DAC can kill 7 logs of L1210 in vivo it is limited to 3-4 log cell kill in vitro (clonogenic assay). DAC can cure mice with L1210 if treatment is early after tumor transplant (day 1) but can cure no mice when treatment is delayed. Neither millimolar thymidine nor 3-deaza-uridine in combination with DAC increase therapeutic effects, which indicates deoxycytidine kinase poor mutants are not responsible for the refractoriness. Combination of DAC and cytoxan or BCNU do lead to cures with late treatment of L1210. These findings suggest that the refractory nature of L1210 to DAC therapy may be due to pharmacological sanctuaries and to dormancy or lantency of L1210 resulting from DAC treatment. We have preliminary in vitro evidence to suggest this latter possibility and are pursuing further evidence.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06108-15 LCHPH

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Mechanism of Action and Mechanism of Resistance of Antitumor Agents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	R.L. Cysyk	Supervisory Pharmacologist,	LCP, NCI
Other:	B. Sinha	Cancer Expert	LCP, NCI
	A. Monks	Visiting Associate	LCP, NCI
	J. Moyer	Staff Fellow	LCP, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Chemical Pharmacology

SECTION
Drug Metabolism Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	2.0	2.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Tiazofurin, a new antitumor agent undergoing clinical evaluation, was found to be an effective inhibitor of nucleoside transport at concentrations achieved in patients' plasma. Inhibition is due to: (a) a direct competition for the transport protein and (b) an indirect effect on uridine/cytidine kinase mediated by an expansion of the UTP pool. 3-Deazauridine, presumably as the nucleoside triphosphate, was found to act intracellularly as a fraudulent allosteric feedback regulator of CPS-II and uridine kinase in cultured L1210 cells. Experiments are underway to determine if similar effects are achieved in vivo and then to exploit this new property of 3-deazauridine for chemotherapeutic benefit. The metabolism of VP-16 and adriamycin was studied with regard to their effects on lipid peroxidation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06148-05 LCHPH

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Endogenous Modifiers of Drug Action

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	R.L. Cysyk	Supervisory Pharmacologist	LCP, NCI
Other:	J. Moyer	Staff Fellow	LCP, NCI
	A. Monks	Visiting Associate	LCP, NCI
	D. Geffen	Medical Staff Fellow	LCP, NCI
	J. Strong	Pharmacologist	LCP, NCI

COOPERATING UNITS *(if any)*

Ohio State University

LAB/BRANCH

Laboratory of Chemical Pharmacology

SECTION

Drug Metabolism Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.0	2.0	3.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

An examination of the salvage of circulating pyrimidines by mouse tissues was completed. Regulation of de novo and salvage mechanisms for pyrimidine biosynthesis in wild type human breast carcinoma cells was compared with cells that overproduce enzymes of the de novo pathway by gene amplification. Efforts to block pyrimidine salvage in vivo were continued. Several new compounds to block uridine transport and/or phosphorylation were designed, synthesized, and evaluated. A preparation of uridine phosphorylase, purified from an overproducing mutant of E. coli, was studied for its effects on circulating uridine concentrations and is currently undergoing evaluation as a chemotherapeutic agent. Efforts to manipulate the hepatic output of purines and pyrimidines were continued. An analog of methylthioadenosine was synthesized to evaluate the role of MTA phosphorylase in the hepatic regulation of circulating adenine.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07131-02 LETM

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Isolation and purification of major lung cell types: Endothelial cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	R. F. Minchin	Visiting Fellow	LETM, NCI
Others:	M. R. Boyd	Associate Director	DTP, NCI
	A. A. del Campo	Bio. Lab. Tech.	LETM, NCI

COOPERATING UNITS *(if any)*:

LAB/BRANCH: Laboratory of Experimental Therapeutics and Metabolism

SECTION: Pharmacology and Toxicology Section

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.4	0.3	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Many pulmonary toxins exert discrete and localized reactions within the lungs suggesting that the heterogeneous population of lung cells vary considerably with respect to interactions with xenobiotics. In order to elucidate the differential effects of various toxins on the lung cell populations, techniques for isolating and characterizing the major cell-types from a number of animal species are being developed. The cell-types of principal interest include the vascular endothelial cells, alveolar type I and type II cells, and the interstitial fibroblasts and pericytes which constitute over 90% of the lung mass. Further, the bronchiolar Clara cells and alveolar macrophages are also of interest because of their known metabolic activities. Isolation and identification of capillary endothelial cells were undertaken because these cells rapidly undergo morphological changes following treatment of animals with several pulmonary toxins such as high oxygen tensions, monocostaline and α-naphthylthiourea. Rabbit lung cells were dispersed into single cell suspensions and subjected to centrifugal elutriation. Various cell fractions were collected at increasing flow rates and the presence of endothelial cells was detected by measuring angiotensin converting enzyme (ACE) and 5-hydroxy-tryptamine metabolism. The endothelial cells were enriched in the first fraction removed from the elutriator indicating that the size of this cell population is small compared to other pneumocytes. Further enrichment was achieved by subjecting the first elutriator fraction to a noncontinuous percoll density gradient. The cell fraction at the 0-20% percoll interface contained the highest ACE activity and represented a 3-5 fold enrichment of the cells. Studies are presently under way to characterize this cell population by both light and electron microscopy.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07132-02 LETM

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 chererters or less. Title must fit on one line between the borders.)*: Paraquat-induced biochemical changes in lung: Effect on the polyamine system

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	R. F. Minchin	Visiting Fellow	LETM, NCI
Others:	G. Hanau	Stay-in-School	LETM, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH: Laboratory of Experimental Therapeutics and Metabolism

SECTION: Pharmacology and Toxicology Section

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.6	0.2	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Several studies have shown that the pulmonary toxin paraquat can modify many biological systems in the lung including DNA synthesis and repair, pyridine dinucleotide balance, glutathione status, glucose utilization and prostaglandin synthesis. Paraquat appears to be accumulated into lung tissue by a process that actively takes up endogenous polyamines. These observations suggested that paraquat may bind to similar biological sites as the polyamines, consequently modifying biochemical processes under polyamine regulation. Equilibrium dialysis and thermal denaturation studies indicated that paraquat reversibly bound to calf thymus DNA leading to a stabilization of the macromolecule. Two binding sites were apparent, defined by independent binding affinities. Putrescine only displaced paraquat from the low-affinity sites. Other studies have shown that paraquat can alter polyamine biosynthesis in vitro (100,000 g lung supernatant) by a process independent of its ability to generate toxic oxygen metabolites. Paraquat attenuated ornithine decarboxylase activity and this was reversed by the addition of putrescine. The herbicide inhibited S-adenosylmethionine decarboxylase in a dose-dependent manner and this inhibition was not altered by the addition of superoxide dismutase. The exact kinetics of paraquat interaction with DNA, ornithine decarboxylase and S-adenosylmethionine decarboxylase are presently under investigation. However, these studies suggest that paraquat is capable of competing for similar biological sites as the endogenous polyamines. Further studies using other 4,4-dipyridyl analogs both in vitro and in vivo should establish whether these compounds are useful antagonists of polyamine-regulated cellular activities.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07133-02 LETM

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Reductive metabolism of nitrofurantoin in lung

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	R. F. Minchin	Visiting Fellow	LETM, NCI
Others:	P. Ho	Summer Student	LETM, NCI
	M. R. Boyd	Associate Director	LETM, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Experimental Therapeutics and Metabolism

SECTION

Pharmacology and Toxicology Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.4	0.2	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Nitrofurantoin is an antibacterial agent with numerous reported occurrences of pulmonary injury in animals and man. Previous studies indicated that nitrofurantoin is enzymatically reduced in lung microsomal preparations to an unstable reactive anion which has been implicated as a possible cause of the nitrofurantoin-induced lung toxicity in vivo. The anion radical is thought to reduce oxygen to superoxide which can subsequently react with cellular constituents. Previous experiments using isolated perfused rat lungs have shown that intact lung can reduce nitrofurantoin to at least 2 stable metabolites and reactive intermediate(s) capable of binding to tissue macromolecules. Overall metabolism was inversely proportional to oxygen tension although measurable metabolism levels were seen in the presence of 95% O_2. Recent studies have compared the relative rates of nitrofurantoin metabolism in rat lung and liver 9000 g supernatants. The 9000 g supernatant was used because previous studies have shown that both microsomal and cytosolic enzymes are responsible for the metabolism of nitrofurantoin. Liver had a much greater capacity for nitrofurantoin reduction under both aerobic and anaerobic conditions. Both organs generated a minimum of 4 metabolites that were qualitatively similar but quantitatively different. Metabolism to stable products was inhibited by oxygen and was not inducible with either phenobarbital of 2,3,7,8-tetrachlorodibenzo-p-dioxin. No evidence for oxidative metabolism in either organ was seen. Menadione, indomethacin and piperonyl butoxide had no effect on nitrofurantoin metabolism. The xanthine oxidase inhibitor, allopurinol, completely inhibited anaerobic metabolism in the lung but not in the liver. Under aerobic conditions, allopurinol decreased the generation of superoxide by nitrofurantoin in lung by 75-80% but by only 20-25% in the liver. These studies have shown that the lung and liver differ in their ability to metabolize nitrofurantoin and suggest that different enzymatic systems are responsible for the reduction of the drug in the two organs. Whether these differences are related to the organ-selective toxicity of nitrofurantoin is presently under investigation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07134-02 LETM

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: In situ lung perfusion as a means to treat pulmonary cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	R. F. Minchin	Visiting Fellow	LETM, NCI
Others:	H. M. Schuller	Visiting Scientist	LETM, NCI
	M. R. Boyd	Associate Director	DTP, NCI

COOPERATING UNITS *(if any)*

Medical College of Wisconsin, Milwaukee, WI (M. R. Johnston, C. A. Dawson and C. Christiansen)

LAB/BRANCH: Laboratory of Experimental Therapeutics and Metabolism

SECTION: Pharmacology and Toxicology Section

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.15	0.15	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project investigates the feasibility of treating non-resectable pulmonary cancers by perfusing the lungs in isolation with high concentrations of anti-cancer agents. A study was initially undertaken to investigate the kinetics of doxorubicin, an anticancer agent active against sarcoma, in in situ perfused dog lungs. The procedure entailed inserting cannulae into the left pulmonary artery and left venous return, effectively isolating the left lobes from the systemic circulation. A wide range of perfusate doxorubicin concentrations was studied in order to determine the rate of drug uptake and retention in the lung tissue. These studies have lead to a Phase I clinical trial utilizing the hemiperfusion technique in metastatic sarcoma patients. The surgical and perfusion procedures were successfully performed in all the patients examined to date. However, in human lung, doxorubicin accumulation was considerably slower than in the dogs. The studies utilizing in situ hemiperfusion of the lungs supported the concept that technique may be useful to treat certain lung cancers. A total lung perfusion technique was then established and the physiological and biochemical effects of this procedure were examined in dogs. Total bypass and lung perfusion (without drug) for up to 60 min produced no surgical complications. Indicator dilution techniques suggested no acute or chronic (up to 8 weeks post-perfusion) damage occurred to the lungs and these results were supported by histopathology of the lung tissue. Studies are presently under way to investigate the kinetics and toxicity of various candidate antitumor agents in the total lung perfusion model.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07135-02 LETM

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Enzyme kinetics of acetylaminofluorene metabolism in animal and man

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	R. F. Minchin	Visiting Fellow	LETM, NCI
Others:	M. R. Boyd	Associate Director	DTP, NCI

COOPERATING UNITS *(if any)*

Laboratory of Experimental Carcinogenesis, Division of Cancer Etiology, NCI (M. E. McManus, S. S. Thorgeirsson and D. Schwartz)

LAB/BRANCH: Laboratory of Experimental Therapeutics and Metabolism

SECTION: Pharmacology and Toxicology Section

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Considerable evidence indicates that differences in metabolic processing of chemical toxins are critical in determining both species and organ sensitivity to individual compounds. The microsomal cytochrome P-450 system catalyzes the oxidation of a variety of substrates and consists of a family of isozymes supported by other reductase proteins. Previous studies characterized the cytochrome P-450 system using the carcinogen acetylaminofluorene (AAF) which is oxidized in the 1, 3, 5, 7, 9 position on the fluorene ring and on the nitrogen. In addition, the effects of a variety of inducers and inhibitors on the kinetics of AAF oxidation in rat and rabbit liver microsomes were examined. More recent studies examined AAF metabolism by control and induced rabbit liver microsomes and by 6 highly purified cytochrome P-450 isozymes (forms 1, 3b, 3c, 3v, 4 and 6) from rabbit liver. Only the formation of 7-hydroxy AAF showed biphasic kinetics, indicative of metabolism by multiple forms of cytochrome P-450, whereas formation of 1-, 3-, 5- and N-hydroxy AAF were monophasic. The kinetics of N-hydroxylation was almost identical with control and induced microsomes and with form 4 of cytochrome P-450. All isozymes examined oxidized AAF in the seven position although Km's and Vmax's varied considerably between forms. AAF metabolism was also examined in human liver microsomes and compared with the hydroxylation of debrisoquine, a substrate with documented polymorphic metabolism in humans. No correlation between AAF metabolism, cytochrome P-450 levels or dibrisoquine 4-hydroxylation was seen. However, the rate of formation of N-, 1-, 3-, 7- and 9-hydroxy AAF appeared polymorphic suggesting the presence of two populations of metabolizers among the human subjects examined. The hydroxylation of AAF also did not correlate with bufuralol oxidation or aldrin epoxidation. These studies have further characterized the differential metabolism of AAF by hepatic cytochrome P-450 isozymes and indicate that this substrate may be a useful proble for studying the role of specific isozymes in xenobiotic metabolism.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07136-02 LETM

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Localized production of reduced oxygen species in the lung

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	R. F. Minchin	Visiting Fellow	LETM, NCI
Others:	M. R. Boyd	Associate Director	DTP, NCI
	A. A. del Campo	Bio. Lab. Tech.	LETM, NCI

COOPERATING UNITS *(if any)*:

LAB/BRANCH: Laboratory of Experimental Therapeutics and Metabolism

SECTION: Pharmacology and Toxicology Section

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.35	0.25	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In the lung, several enzyme systems including monooxygenase activity have been found to be localized within discrete cell populations. Consequently, several pulmonary toxins are particularly damaging to select cell-types. In order to study where toxic reduced oxygen species such as superoxide or hydrogen peroxide are produced within the lung, a histochemical technique utilizing the heavy metal, cerium, has been investigated. Cerium reacts with superoxide/hydrogen peroxide to produce a precipitate that can be readily visualized by electron microscopy. The technique has been applied mainly in rat lung slices, isolated perfused rat lung and isolated rat lung cells to investigate localized production of hydrogen peroxide. Extensive studies using Ce/H_2O_2 in the presence of a range of antioxidant enzymes and superoxide traps were undertaken in order to characterize the interaction of cerium with reduced oxygen. The rate of this reaction was biphasic, pH-dependent and inhibited by ascorbic acid, superoxide dismutase and albumin but not by ethanol or mannitol. In rat lung slices, cerium-derived electron dense bodies were seen principally around the alveolar type II cells. These bodies were diminished in the presence of catalase but superoxide dismutase produced no apparent effect. Spectral X-ray microanalysis confirmed the presence of cerium and also indicated the presence of phosphorus suggesting that at least some of the electron-dense staining arose from the presence of inorganic phosphorus. No cerium was detected on membranes of alveolar type I or endothelial cells, or in the cytoplasm and nucleus of the alveolar type II cells. The exact cause of the highly localized precipitation of cerium around the type II cells is presently unknown.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07138-02 LETM

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Mechanism of MeCCNU nephrotoxicity

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	R. A. Kramer	Guest Worker	LETM, NCI
Others:	M. R. Boyd	Associate Director	DTP, NCI
	H. Schuller	Visiting Scientist	LETM, NCI
	M. G. McMenamin	Bio. Lab. Tech.	LETM, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH: Laboratory of Experimental Therapeutics and Metabolism

SECTION: Pharmacology and Toxicology Section

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.95	0.45	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Studies completed, under way or planned include: a) in vivo studies of the effect of drug metabolism inhibitors or inducers on the metabolism, distribution, covalent binding and nephrotoxicity of MeCCNU in F344 rats, b) in vitro studies on the metabolism and covalent binding of MeCCNU by rat liver or kidney microsomes, and c) studies on the role of endogenous GSH as a protective factor in modulating the nephrotoxicity of MeCCNU.

These studies demonstrate that reactive metabolites and/or degradation products of MeCCNU are accumulated preferentially in kidney and that pretreatment of rats with an inhibitor of cytochrome P-450, piperonyl butoxide, decreased the metabolism and covalent binding of MeCCNU to liver and kidney macromolecules and ameliorated MeCCNU nephrotoxicity. Furthermore, rat liver, but not kidney, microsomes catalyzed the alkylation of chloroethyl-derived MeCCNU to proteins by a reaction that was both oxygen and NADPH dependent, and was inhibited by the addition of either piperonyl butoxide or glutathione to the reaction medium. In contrast, rat liver microsomes metabolized the cyclohexyl moiety of MeCCNU to products with less carbamylating activity than was observed by the non-enzymatic degradation of MeCCNU. Endogenous glutathione appears to play a major protective role against MeCCNU toxicity in the kidney.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07139-02 LETM

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: In vivo models of anticancer drug-induced nephrotoxicity

PRINCIPAL INVESTIGATOR *(List other professionel personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	R. A. Kramer	Guest Worker	LETM, NCI
Others:	M. R. Boyd	Associate Director	DTP, NCI
	J. H. Dees	Cancer Expert	LETM, NCI
	M. G. McMenamin	Bio. Lab. Tech.	LETM, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH: Laboratory of Experimental Therapeutics and Metabolism

SECTION: Pharmacology and Toxicology Section

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.65	0.45	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the spece provided.)*

Studies completed, under way or planned on the target tissue toxicity of anticancer drugs include: a) the development of in vivo models of nephrotoxicity; b) elucidation of the biochemical mechanisms underlying the delayed and progressive nephropathy of MeCCNU; c) characterization and mechanism of the acute nephrotoxicity of high dose chlorozotocin or streptozotocin; d) role of bioreduction in mediating the nephrotoxicity of mitomycin C; and e) comparative studies on the nephrotoxicity of the newer cis-platinum analogs.

The initial emphasis has been primarily on nitrosoureas. We have developed a reliable model of MeCCNU renal damage in BDF mice and Fischer 344 rats and have shown that histopathological changes produced by the drug are closely paralleled by marked changes in biochemical parameters measurable in vitro in kidney slices, as well as by certain in vivo renal function tests. The Fischer rat also was shown to be a relevant animal model for studying the nephrotoxicity of other nitrosoureas. For example, high doses of either streptozotocin or chlorozotocin were found to be acutely nephrotoxic, whereas, low doses of chlorozotocin resulted in a chronic progressive nephropathy similar to that of MeCCNU. Unlike MeCCNU, however, chlorozotocin lacks carbamylating activity suggesting that the nephrotoxicity of the nitrosoureas is a result of the alkylating capabilities of the compounds. The overall goals of these studies are to: a) elucidate the chemicobiologic events that underlie the nephrotoxicity of the nitrosoureas and b) develop improved methods for predicting, monitoring or treating such reactions in patients.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07140-02 LETM

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

BCNU-induced pulmonary toxicity in F344 rats

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	A. C. Smith	Guest Worker	LETM, NCI
Others:	H. M. Schuller	Visiting Scientist	LETM, NCI
	M. R. Boyd	Associate Director	DTP, NCI
	G. P. Kim	Bio. Lab. Aid	LETM, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Experimental Therapeutics and Metabolism

SECTION

Pharmacology and Toxicology Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.15	1.05	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

BCNU, an alkylating antitumor drug, is a potent inhibitor of GSSG reductase in liver and red blood cells. Since GSSG reductase is responsible for maintaining the intracellular antioxidant defense mechanisms, inhibition of this enzyme by BCNU may ultimately lead or contribute to pulmonary damage. Single doses of BCNU inhibited lung GSSG reductase in a dose- and time-dependent manner. The depression of reductase activity was persistent, lasting up to 8 days after BCNU administration. The multi-dosing BCNU treatment regimen produces a delayed onset interstitial fibrosis in the lung. This treatment regimen also causes a 70% reduction of pulmonary GSSG reductase and a 300% increase in pulmonary GSSG levels. These effects were specific for the lung; there was no marked or persistent inhibition of GSSG reductase or alteration of GSH/GSSG ratio in kidney, liver or heart tissue. The inhibition of pulmonary GSSG reductase by BCNU preceded the onset of marked pulmonary damage. BCNU-induced inactivation of lung GSSG reductase occurred in vitro, required NADPH, and was time- and concentration-dependent. Exogenously added substrate or sulfhydryl compounds were capable of decreasing the amount of enzyme inactivated by BCNU. The distribution of ^{14}C-BCNU in F344 rats demonstrated that BCNU was not preferentially accumulated in pulmonary tissue either as total ^{14}C (parent drug and metabolites) or as radioactivity covalently bound to cellular macromolecules. These studies demonstrate that there is a preferential destruction of lung GSSG reductase by BCNU which precedes the development of severe lung toxicity and that this preferential BCNU-induced lung toxicity is not due to a preferential accumulation in lung tissue.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07142-02 LETM

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on ona line between the borders.)*: Isolation and characterization of reactive metabolites of toxic furans

PRINCIPAL INVESTIGATOR *(List other professional personnal below tha Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	V. Ravindranath	Visiting Fellow	LETM, NCI
Others:	M. R. Boyd	Associate Director	DTP, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH: Laboratory of Experimental Therapeutics and Metabolism

SECTION: Pharmacology and Toxicology Section

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.3	0.3	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Usa standard unreduced type. Do not exceed the space provided.)*

The molecular mechanisms involved in the metabolic activation of certain cytotoxic furans, namely 4-ipomeanol, a natural product isolated from mouldy sweet potatoes, and 3-methylfuran (3-MF), an atmospheric pollutant, are being investigated. Not only does the environmental occurrence of certain furans have possible major toxicological significance but also there is also a growing interest in some furan derivatives as potential antitumor agents. Oxygen and NADPH dependent metabolic activation of these furans results in the formation of highly electrophilic metabolites that alkylate microsomal proteins. The pulmonary toxin, 3-MF, and 2-methylfuran (2-MF), a natural product present in cigarette smoke, coffee and many foods, are activated by microsomal monooxidases to reactive electrophiles that bind to tissue macromolecules. Using semicarbazide (SC) as a trapping reagent, acetyl acrolein (AA) and methyl butenedial (MB) were isolated as products of microsomal oxidation of 2-MF and 3-MF, respectively. A comparison of the covalent binding of [^{3}H]-3-MF and the amounts of MBD disemicarbazone produced in microsomal incubation in the presence and absence of NADPH and SC, revealed an inverse relationship between the two measures. NADPH dependent covalent binding of 3-MF was strongly inhibited by SC, presumably by trapping the reactive dialdehyde intermediate (MB) before it could react with tissue macromolecules. Although the initial formation of these metabolites was dependent on NADPH, the binding of synthetic ^{14}C-AA to microsomal protein was extremely rapid and was not further enhanced by NADPH. Thus, the unsaturated aldehydes, AA and MB, appear to be the principal reactive intermediates of 2-MF and 3-MF that are bound covalently to tissue macromolecules in these preparations. Moreover, since the covalent binding of reactive material is directly correlated with toxicity, the dialdehyde is possibly responsible both for target tissue alkylation and for toxicity produced by the parent furan *in vivo*.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07157-01 LETM

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Distribution of monooxygenase activity in isolated rabbit lung cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	R. F. Minchin	Visiting Fellow	LETM, NCI
Others:	M. R. Boyd	Associate Director	DTP, NCI

COOPERATING UNITS *(if any)*

Laboratory of Experimental Carcinogenesis, Division of Cancer Etiology, NCI (M. E. McManus, D. Schwartz and S. S. Thorgeirsson)

LAB/BRANCH: Laboratory of Experimental Therapeutics and Metabolism

SECTION: Pharmacology and Toxicology Section

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.4	0.4	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

It has been demonstrated that the localization of the cytochrome P-450 system to select cell-types in the lungs predisposes those cells to toxicity by xenobiotics requiring metabolic activation. Regiospecific hydroxylation of 2-acetylamino-fluorene (AAF) was used to monitor monooxygenase activity in isolated rabbit lung cells. Following isolation, the cells were separated into 7 different fractions according to size by centrifugal elutriation. Macrophages were recovered from the lungs by lavage and examined in parallel with the parenchymal cell populations. The resulting fractions were assayed for AAF hydroxylase activity and were examined for the presence of endothelial cells (angiotensin converting enzyme), alveolar type II cells (modified Papanicolaou stain), polymorphonuclear leukocytes (modified Papanicolaou stain), bronchiolar Clara cells (nitroblue tetrazolium stain) and ciliated cells (phase contrast microscopy). Highest hydroxylase activities were seen in the cell fraction containing the largest percentage of Clara cells. The activity profiles provided evidence for a population of cells not correlating with either alveolar type II cells or Clara cells but possessing substantial monooxygenase activity. The alveolar macrophage almost exclusively hydroxylated AAF in the 9 position and the cell fraction containing the higher percentage of endothelial cells metabolized AAF the least. Pretreatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) preferentially induced the 7-hydroxylation of AAF and either did not alter or decreased the rate of formation of the other hydroxy metabolites. An exception was seen in fraction 1 where TCDD induced the hydroxylation of AAF to all products except 3-hydroxy AAF. Analysis of the metabolite profiles over the 8 cell fractions used in the present study suggested that at least 4 monooxygenases may be present in rabbit lung.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07158-01 LETM

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 charecters or less. Title must fit on one line between the borders.)*
Nitrofurantoin pharmacokinetics in control and vitamin E-deficient rats

PRINCIPAL INVESTIGATOR *(List other professionel personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	R. F. Minchin	Visiting Fellow	LETM, NCI
Others:	M. R. Boyd	Associate Director	DTP, NCI

COOPERATING UNITS *(if any)*
Laboratory of Chemical Pharmacology, Division of Intramural Research, NHLBI, (H. Sasame)

LAB/BRANCH
Laboratory of Experimental Therapeutics and Metabolism

SECTION
Pharmacology and Toxicology Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.4	0.4	0.0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The antibacterial drug nitrofurantoin (NF) has previously been shown to undergo one electron reduction in pulmonary microsomes with the subsequent production of oxygen metabolites and peroxidation of membrane lipids. A number of studies have attempted to relate the pulmonary toxicity of NF to the in vivo generation of toxic oxygen metabolites. Animals depleted of vitamin E have been shown to be markedly more susceptible to NF-induced lung damage than control animals. Other work has suggested that vitamin E represents an important antioxidant in the lungs and may be critical in protecting the organ against oxygen-mediated peroxidation of cellular unsaturated lipids. These results lend support to a role of toxic oxygen metabolites in NF pulmonary toxicity. Because vitamin E deficiency caused such a striking increase in the toxicity of NF, a study was undertaken to examine the pharmacokinetics of the drug in control and vitamin E deficient rats. Nitrofurantoin was rapidly absorbed following subcutaneous injection and was cleared from all tissues examined (blood, lung, liver and kidney) in a biphasic manner. Significant metabolism of the drug was observed and the disposition of NF metabolites was qualitatively similar to that of the parent compound. The most apparent difference between control and vitamin E deficient animals was a significant increase in tissue metabolite levels 4 to 16 hr post treatment. Unchanged NF was also elevated in all tissues examined by 16 hr in the vitamin E deficient animals. Urinary excretion of NF and metabolites over 16 hr accounted for 68% and 35% of the total dose in control and vitamin E deficient rats. The present study illustrates a marked alteration in NF disposition in animals fed a diet lacking vitamin E, compared to control animals. The observed alterations appear to be related to a decreased renal clearance of both NF and metabolites. These data provide an alternative explanation for the previously observed enhanced pulmonary toxicity of NF in vitamin E deficient animals.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07159-01 LETM

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Reactive GSH conjugates: Toxicology and novel chemotherapeutic applications

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: R. A. Kramer Guest Worker LETM, NCI

Others: M. R. Boyd, Associate Director, DTP, NCI; J. H. Smith, Staff Fellow; M. A. Smith, Staff Fellow; S. S. Lau, Staff Fellow; V. Ravindranath, Visiting Fellow; W. C. Hubbard, Cancer Expert; J. B. McMahon, Cancer Expert; M. G. McMenamin, Bio. Lab. Tech.; and C. Scheltema, Co-Op Student, NCI, Bethesda, Maryland

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Experimental Therapeutics and Metabolism

SECTION
Pharmacology and Toxicology Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.1	0.9	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Studies completed, under way or planned include investigations on the: a) nephrotoxocity and potential antitumor activity of reactive GSH conjugates [e.g., S-2-chloroethyl GSH; diglutathionyl bromohydroquinone and S-(1,1,2,3,4-pentachloro 1:3-butadienyl)-GSH]; b) role of hepatic metabolism in the formation and subsequent transport of these conjugates to the kidney; c) γ-glutamyl cycle and mercapturic acid biosynthetic pathway in normal renal and in γ-GT positive tumor cells.

Initial emphasis has been primarily on determining whether chloroethylnitrosoureas (i.e., MeCCNU, chlorozotocin) manifest their nephrotoxicity via the formation of reactive GSH conjugates (i.e., S-2-chloroethyl GSH). Preliminary data have shown that pretreatment with inhibitors of γ-glutamyltranspeptidase activity protected against MeCCNU nephrotoxicity in vivo. Pretreatment with an inhibitor of GSH synthesis (BSO) resulted in a marked decrease in liver and kidney GSH, and to a corresponding increase in covalent binding by chloroethyl labeled MeCCNU in liver. However, covalent binding to kidney protein or DNA was decreased by nearly 50%. An unidentified metabolite of MeCCNU has been isolated from the bile of MeCCNU treated rats. This metabolite was found to be toxic to a tumor cell line possessing high γGT activity. In vitro studies utilizing rat liver microsomes have demonstrated the formation of chloroethyl-derived GSH conjugates of MeCCNU which were formed by an NADPH dependent reaction. These studies provide preliminary evidence which suggests that MeCCNU is metabolized to a GSH conjugate which may produce nephrotoxicity and possess antitumor activity.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07161-01 LETM

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: In vivo studies on the toxicity of alkylfurans

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	V. Ravindranath	Visiting Fellow	LETM, NCI
Others:	M. G. McMenamin	Bio. Lab. Tech.	LETM, NCI
	M. R. Boyd	Associate Director	DTP, NCI

COOPERATING UNITS *(if any)*:

LAB/BRANCH: Laboratory of Experimental Therapeutics and Metabolism

SECTION: Pharmacology and Toxicology Section

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.6	0.5	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The mechanisms involved in the metabolic activation and toxicity of 2-methylfuran (2-MF), a naturally occurring cytotoxic furan found in cigarette smoke and coffee are being investigated. 2-MF and 3-methylfuran are bioactivated in vitro by microsomal mixed function oxidases to acetylacrolein and methylbutenedial, respectively, that bind covalently to microsomal protein. Unsaturated aldehydes can react with both protein and DNA either via Michael addition across the activated double bond or nucleophilic addition to the aldehyde.

Following administration of 2-[(^{14}C)methyl]furan to rats, extensive covalent binding of label to macromolecules in liver, lungs and kidney was observed. Smaller amounts were bound to tissues with little or no known mixed function oxidase activity. Maximal covalent binding to both protein and DNA was observed in the liver, the target organ where toxicity is manifested. Liver GSH levels decreased by a third, half an hour after administration of 2-MF indicating the formation of electrophilic metabolites. Pretreatment with various inhibitors and inducers of metabolism showed that phenobarbital potentiated toxicity of 2-MF and was followed by increased urinary excretion of label, while 3-methylcholanthrene or piperonyl-butoxide did not markedly alter the toxicity of 2-MF. Pretreatment with buthionine sulfoximine (BSO), a GSH depletor and a chemosensitizing agent, while decreasing covalent binding, also decreased toxicity, whereas diethylmaleate, also a GSH depletor, increased both covalent binding and toxicity of 2-MF. BSO, which depletes GSH levels by inhibiting cysteine synthetase is known to enhance cysteine levels in tissues. Thus, BSO probably decreases covalent binding by trapping the reactive intermediate as the stable cysteine conjugate.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07162-01 LETM

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Role of arachidonic acid metabolism in human lung cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	W. C. Hubbard	Cancer Expert	LETM, NCI
Others:	S. S. Lau	Staff Fellow	LETM, NCI
	J. B. McMahon	Cancer Expert	LETM, NCI
	H. M. Schuller	Visiting Scientist	LETM, NCI
	M. R. Boyd	Associate Director	DTP, NCI
	K. E. Greene	Bio. Lab. Tech.	LETM, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH: Laboratory of Experimental Therapeutics and Metabolism

SECTION: Pharmacology and Toxicology Section

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	0.9	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Arachidonic acid is the precursor of a large number of compounds possessing diverse activities. Known products of arachidonic acid include the prostaglandin thromboxanes, leukotrienes and hydroxyeicosanoids. One metabolite of arachidonic acid, prostaglandin E_2 (PGE_2), has been implicated as a mediator of hypercalcemia associated with certain lung cancers (Seyberth et al., N. Engl. J. Med. 239: 1228, 1975). The luekotrienes participate in the initiation of immune and inflammatory responses (Lewis and Austen, J. Clin. Invest. 73: 889, 1984) and thus could play a role in host defense mechanisms in human lung cancer. Studies of the metabolism of arachidonic acid were undertaken to determine the pathways of arachidonic acid metabolism in human lung cancer cells and the relevance of arachidonate metabolism in human lung cancer.

Non-small cell carcinomas of the lung (NSCCL) and small cell carcinomas of the lung (SCCL) were incubated with either ^{14}C-labeled arachidonic acid or with ^{14}C-labeled arachidonic acid in the presence of the calcium ionophore A23187. The major prostaglandin endoperoxide synthetase (PES) metabolite isolated from NSCCL has been tenatatively identified as PGE_2. SCCL do not appear to contain significant levels of PES. Analysis of the extracts from SCCL and NSCCL for the presence of lipoxygenase products of arachidonic acid are being performed.

Futher studies of the metabolism of arachidonic acid by human cancer cells will continue to determine the regulation and extent of arachidonic acid metabolism in the presence and absence of different inhibitors and stimulators of the various pathways of arachidonate metabolism. Additional studies in tumor-bearing nude mice will be performed to determine whether or not the profile of arachidonate metabolism in human lung cells in vitro accurately reflect arachidonate metabolism in vivo.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07163-01 LETM

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Xenobiotic metabolism by prostaglandin endoperoxide synthetase (PES)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	S. S. Lau	Staff Fellow	LETM, NCI
Others:	W. C. Hubbard	Cancer Expert	LETM, NCI
	M. R. Boyd	Associate Director	DTP, NCI
	K. E. Greene	Bio. Lab. Tech.	LETM, NCI

COOPERATING UNITS *(if any)*: Laboratory of Chemical Pharmacology, NHLBI, NIH (T. J. Monks)

LAB/BRANCH: Laboratory of Experimental Therapeutics and Metabolism

SECTION: Pharmacology and Toxicology Section

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.9	0.6	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The site of toxicity of a number of xenobiotics and antitumor agents requiring metabolic activation is distributed in tissues containing very little P-450 monooxygenase activity. Because of the ubiquitous distribution of the prostaglandin endoperoxide synthetase (PES) system and the ability of this system to catalyze the cooxidation of xenobiotics to carcinogenic, mutagenic or other reactive species, it has been implicated to play a significant role in the metabolism of xenobiotics. We have initiated studies on the metabolism of 2-bromohydroquinone (BHQ), a compound which undergoes metabolic activation apparently independent of the P-450 monooxygenase system. BHQ is converted to reactive metabolites when incubated with PES from rat renal papilla tissue in the presence of arachidonic acid (0.08 mM). Aspirin and indomethacin, inhibitors of the fatty acid cyclooxygenase component of PES and methimazole and propylthiouracil, inhibitors of the hydroperoxidase component of PES significantly decreased the formation of reactive metabolites of BHQ in rat renal papilla.

The nephrotoxicity of BHQ in vivo in rats was not inhibited by the fatty acid cyclooxygenase (FAC) inhibitors aspirin and indomethacin. However, while aspirin and indomethacin were effective in inhibiting FAC, these compounds do not inhibit either the formation of hydroperoxy fatty acids via lipoxygenase pathways or the hydroperoxidase component of PES. Since lipoxygenase derived fatty acid hydroperoxides may be substrates for the hydroperoxidase, cooxidation of BHQ in vivo could occur even in the absence of prostaglandin biosynthesis. The role of the hydroperoxidase component of the PES system and other hydroperoxidase enzymes are currently under investigation.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07145-02 LETM

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Pathology of BCNU-induced lung injury

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	H. M. Schuller	Visiting Scientist	LETM, NCI
Others:	A. C. Smith	Guest Worker	LETM, NCI
	M. R. Boyd	Associate Director	DTP, NCI
	M. Gregg	Bio. Lab. Tech.	LETM, NCI

COOPERATING UNITS *(if any)*:

LAB/BRANCH: Laboratory of Experimental Therapeutics and Metabolism

SECTION: Pathology and Ultrastructural Oncology Section

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Histopathology and electron microscopy of lung lesions induced in F344 rats by chronic BCNU treatment showed that the animals developed interstitial fibrosis, emphysema, alveolitis, chronic bronchitis and peribronchitis as well as pneumonia. A serial sacrifice experiment was conducted to study the development of these lesions sequentially. The first changes were detected in alveolar type II cells which exhibited morphological changes suggestive of a disturbed surfactant production. Subsequently, damage of endothelia followed by development of perivascular and alveolar edema became noticeable. This damage to the lung periphery then resulted in the gradual development of fibrosis which became fully manifest by week 20 of BCNU treatment.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07152-01 LETM

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies on Clara cell mediated lung carcinogenesis in vivo

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	H. M. Schuller	Visiting Scientist	LETM, NCI
Others:	J. B. McMahon	Cancer Expert	LETM, NCI
	J. H. Dees	Cancer Expert	LETM, NCI
	M. R. Boyd	Associate Director	DTP, NCI
	M. Gregg	Bio. Lab. Tech.	LETM, NCI
	S. Walton	Bio. Lab. Aid	LETM, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Experimental Therapeutics and Metabolism

SECTION

Pathology and Ultrastructural Oncology Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A number of N-nitrosamines are powerful respiratory tract carcinogens which require metabolic activation in the host organism. This metabolic activation is believed to be mediated by cytochrome P-450 enzymes although unequivocal evidence for this hypothesis has not yet been achieved. An experiment was conducted to investigate the effect of the P-450 enzyme inhibitor, piperonyl butoxide, on the induction of lung tumors which originate from Clara cells in hamsters treated with N-nitrosodiethylamine (DEN). The effect of piperonyl butoxide on covalent binding and distribution of the parent nitrosamine was examined in vivo after 1 dose of ^{14}C-DEN. Moreover, the effect of piperonyl butoxide on the tumor incidence induced by DEN in a chronic study was investigated by histopathology. Piperonyl butoxide significantly inhibited metabolism of DEN in the respiratory tract and inhibited the induction of lung tumors. These data provide the first experimental evidence for cytochrome P-450 enzymes being a crucial factor to the metabolic activation of DEN in vivo.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07153-01 LETM

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Biology of human lung cancer cell lines in vitro

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. B. McMahon	Cancer Expert	LETM, NCI
Others:	H. M. Schuller	Visiting Scientist	LETM, NCI
	M. R. Boyd	Associate Director	DTP, NCI
	M. Falzon	Visiting Fellow	LETM, NCI
	A. del Campo	Bio. Lab. Tech.	LETM, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH: Laboratory of Experimental Therapeutics and Metabolism

SECTION: Pathology and Ultrastructural Oncology Section

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Lung cancer is one of the most common, most lethal, but least treatable diseases. All currently available anticancer drugs are essentially ineffective against most human lung cancers. For the purpose of therapy, lung cancers are generally classified into small cell and non-small cell cancers. With respect to the many different tumor types found in the category of non-small cell cancer, it is difficult to imagine that any one anticancer drug can be effective against all of them. It is the objective of this project to characterize the biology of different types of human lung cancers in vitro by a variety of methods including: scanning and transmission electron microscopy, quantitative image analysis, assays for the activity of a variety of enzymes (e.g., cytochrome P-450, dopa-decarboxylase and production of polypeptide hormones) competence for binding and metabolism of diethylnitrosamine and 4-ipomeanol, and assessment of cytotoxicity of these compounds by colony formation assay and soft agar techniques.

We found that established APUD characteristics do not correlate in several small cell cancer lines after priming with 5-hydroxytryptophan (5-HTP) and may hence not be good markers for this category of lung cancer. The small cell cancer lines studied did not bind and metabolize DEN and 4-ipomeanol, and the compounds did not induce cytotoxicity. In contrast, the non-small cell cancer lines selected on the basis of their cell types (as revealed by electron microscopy) exhibited covalent binding, metabolism and cytotoxicity with the 2 compounds, whereby the cell line with morphological features of Clara cells was the most active. These data exemplify that there is a pronounced specificity among different types of lung cancer when it comes to response to chemicals. It may well be possible to take advantage of such specificity for the development of more targeted anticancer drugs.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07154-01 LETM

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Isolation and selective growth of rodent lung cell types in vitro

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. B. McMahon	Cancer Expert	LETM, NCI
Others:	M. R. Boyd	Associate Director	DTP, NCI
	A. del Campo	Bio. Lab. Tech.	LETM, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH: Laboratory of Experimental Therapeutics and Metabolism

SECTION: Pathology and Ultrastructural Oncology Section

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

It is well established that certain pulmonary toxins and carcinogens act on specific cell types of the rodent lungs. Metabolism studies in vivo, or experiments using whole organ homogenates and fractions, may therefore not be suited to detect metabolic pathways operative in such specific cell types. It is the objective of this project to isolate and selectively grow the major epithelial cell types of the rat and hamster lung and to use them for comparative studies on their biology and response to toxins, carcinogens and anticancer drugs. Type II cells and mucous cells of the rat lung have been successfully isolated as have been hamster type II cells. Efforts are currently being made to isolate hamster neuroendocrine cells. The morphology of the isolated type II and mucous cells has been characterized in detail by scanning and transmission electron microscopy. Comparative experiments are under way on the effect of the pulmonary agents diethylnitrosamine, 4-ipomeanol and BCNU on these cell types.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07102-09 LMCB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Tubulin Structure and Microtubule Formation as Sites for Pharmacologic Attack

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Ernest Hamel	Cancer Expert	LMCB, NCI
Others:	Janendra K. Batra	Visiting Fellow	LMCB, NCI
	Chii M. Lin	Biologist	LMCB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Medicinal Chemistry and Biology

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	2.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The rational development of new antineoplastic agents directed against tubulin, a protein critical for cell division, requires greater understanding of the interactions between the polypeptide subunits of tubulin and its two tightly bound guanine nucleotides. Interactions of ribose- and polyphosphate-modified GDP and GTP analogs with tubulin were examined in a microtubule-associated protein-dependent polymerization system. Although ribose-modified GTP analogs had a reduced affinity for tubulin, several of these nucleotides supported vigorous polymerization reactions by enhancing polymer nucleation, the rate-limiting step in microtubule assembly. Polyphosphate-modified analogs also had a reduced affinity for tubulin, except for guanosine 5'-O-(3-thiotriphosphate), which was a potent nucleotide inhibitor of tubulin polymerization and GTP hydrolysis. The effects of pH and the magnesium cation on the interactions of GDP and GTP with tubulin were examined in detail. In the course of preparing large amounts of microtubule-associated proteins, a protein component was isolated which caused microtubule bundle formation. Several new classes of antimitotic drugs were studied. These included combretastatin, a plant-derived natural product, and two groups of synthetic compounds, 6-benzyl-1,3-benzodioxoles and 5,6-diarylpyridazin-3-ones. Efforts to separate the α and β subunits of tubulin continued.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07104-09 LMCB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
L-Phenylalanine Mustard Cytotoxicity and Therapy

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	David T. Vistica	Pharmacologist	LMCB, NCI
Others:	Barbara P. Vistica	Microbiologist	LMCB, NCI

COOPERATING UNITS *(if any)*
Medicine Branch, NCI

LAB/BRANCH
Laboratory of Medicinal Chemistry and Biology

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Human ovarian carcinoma cells resistant to L-phenylalanine mustard have a 2-3 fold elevated content of the tripeptide glutathione as compared to drug sensitive cells. Reduction of the glutathione content by either nutritional deprivation of L-cysteine or use of DL-buthionine-S, R-sulfoximine, an inhibitor of glutathione biosynthesis, resulted in sensitization of the resistant cell.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07156-01 LMCB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Differentiation of Human Leukemia Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Theodore R. Breitman	Chemist	LMCB, NCI
Other:	Masue Imaizumi	Visiting Fellow	LMCB, NCI
	Linda Shonk	Biologist	LMCB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Medicinal Chemistry and Biology

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.8	2.8	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The availability of tissue culture cell lines has made it possible to study the regulation of proliferation and differentiation of specific hematopoietic cell types and the effects on these cells of known or suspected mediators and modulators. It was found previously in this laboratory that retinoic acid is a potent inducer of terminal differentiation of the human promyelocytic cell line, HL-60, and the human monoblast- and monocyte-like cell lines, U-937 and THP-1. In addition retinoic acid was found to induce differentiation of fresh cells in primary culture of patients with acute promyelocytic leukemia. While retinoic acid alone is capable of inducing terminal differentiation combinations of a physiological concentration of retinoic acid (10 nM) and either cAMP inducing agents (e.g., cAMP, prostaglandin E, or cholera toxin) or the conditioned medium from either activated T-cells or human leukemic T-cell lines were synergistic in inducing differentiation of HL-60. An activity called "differentiation inducing factor" or DIF has been purified to homogeneity from this conditioned medium. In addition to DIF, immune interferon-gamma has also been identified as having differentiation inducing activity. Studies with combinations of retinoic acid and recombinant interferongamma have yielded results that are identical to those obtained with retinoic acid and DIF. These results suggest that these combinations may have utility in the treatment of patients with some leukemias.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07109-08 LMCB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Effect of Anticancer Drugs on Cell Viability and the Synthesis of Nucleic Acids

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Robert I. Glazer	Head	LMCB, NCI
Others:	Mrunal S. Chapekar	Visiting Fellow	LMCB, NCI
	Marvin B. Cohen	Staff Fellow	LMCB, NCI
	Kathleen D. Hartman	Chemist	LMCB, NCI
	Masaaki Iigo	Visiting Fellow	LMCB, NCI
	Ester Zylber-Katz	Visiting Scientist	LMCB, NCI
	Marion C. Knode	Biologist	LMCB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Medicinal Chemistry and Biology

SECTION
Applied Pharmacology Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.5	4.5	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The mechanism of action of three classes of antitumor drugs will be assessed in human tumor cells in tissue culture, and will include studies of ribosomal RNA processing, transcription, methylation of RNA and DNA and protein phosphorylation. The first project deals with nucleoside antimetabolites as exemplified by the pyrrolopyrimidines tubercidin, toyocamycin and sangivamycin, the carbocylic cyclopentene analog of adenosine, neplanocin-A, and the pyrimidines arabinosyl-5-azacytosine, 2'-deoxyazacytidine, azacytidine, and 5-fluorouridine. The second study involves examining the cytocidal activity of human immune interferon both alone and in combination with double-stranded RNA, and analogs of the interferon-induced 2',5'-oligoadenylates as prototypes of a new class of antitumor drugs. Chemically modified 2',5'-oligoadenylates will be studied for their ability to activate latent endoribonuclease and inhibit 2',5'-oligo-(A) phosphodiesterase.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07155-01 LMCB

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cellular and Molecular Pharmacology of Anthracycline Anticancer Drugs

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Robert I. Glazer	Supervisory Pharmacologist	LMCB, NCI
Others:	Ester Zylbur-Katz	Visiting Scientist	LMCB, NCI
	Marian C. Knode	Biologist	LMCB, NCI
	Kathleen Hartman	Chemist	LMCB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Medicinal Chemistry and Biology

SECTION

Applied Pharmacology Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2	1	1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the spece provided.)*

Putative cell membrane targets will be examined as possible mediators of the cytotoxicity of anthracycline anticancer drugs such as Adriamycin. Cell membrane-bound protein kinase C (calcium-phospholipid-dependent protein kinase) and its associated phorbol diester receptor will be measured for its activity and ability to bind radiolabeled phorbol diester. The ability of phorbol diesters to alter the cytotoxicity to human colon carcinoma cell line HT-29 and promyelocytic leukemia HL-60 will also be measured by a clonogenic assay. Possible cellular targets such as the phosphorylation of microfilaments and other peptides associated with the activity of protein kinase C will be examined electrophoretically using immunochemical procedures.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07122-04 LMCB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Biochemical & Pharmacologic Studies with Oncolytic Nucleosides

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	David A. Cooney	Chief, Medical Officer	LMCB, NCI
Others:	Hiremagalur N. Jayaram	Pharmacologist	LMCB, NCI
	Gurpreet Ahluwalia	Visiting Fellow	LMCB, NCI
	Yvonne Wilson	Chemist	LMCB, NCI
	Maha Dalal	Chemist	LMCB, NCI

COOPERATING UNITS *(if any)*
Medicine Branch, NCI (R. Ozols); Navy Medical Oncology Branch, NCI (J.D. Minna and and D. Carney); Pediatric Oncology Branch, COP, DCT, NCI (D.G. Poplack).

LAB/BRANCH
Laboratory of Medicinal Chemistry and Biology

SECTION
Biochemistry Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.0	3.0	2.0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Section has been examining factors governing the responsiveness of neoplastic cells to the oncolytic nucleosides: tiazofurin, selenazofurin and arabinosyl-5-azacytidine (araAC). In addition, studies were initiated on the mechanism of action of the discreet drug NSC 336628D. I. In susceptible cells, tiazofurin and selenezofurin are metabolized to TAD and SAD, dinucleotides congeneric to NAD. The phosphodiester linkages of TAD and SAD are susceptible to enzymatic cleavage. This past year, the enzyme catalyzing this cleavage was purified 200-fold from murine and human tumor cells preparatory to a clarification of its properties. At physiologic pH, this enzyme decomposes TAD to tiazofurin-5'-monophosphate and AMP; NAD is not attacked, but does inhibit the degradation of TAD. Also observed was a pronounced tendency of tumor cells resistant to tiazofurin to degrade TAD more rapidly than their sensitive counterparts. II. AraAC is an unstable triazene nucleoside combining the structural elements of two other clinically useful molecules: arabinosyl cytosine and 5-azacytidine. In vivo, AraAC is extensively phosphorylated and incorporated into DNA; as a temporal consequence of these metabolic fates, DNA synthesis is brought to a halt. Although the triazine base already incorporated into nucleic acids undergoes ring opening and further release of formate, no evidence for strand breaks has been obtained by alkaline-elution analysis. III. NSC 336628D is a novel discreet oncolytic agent curative of the L1210 leukemia. Versus L1210 cells in culture, the agent exhibits a median inhibitory concentration of ~7 μM. As adjudged by soft-agar cloning, this concentration kills 50% of the cells exposed to it within 1 hour. Simultaneously, nucleic acid biosynthesis and the phosphoribosylation reactions of de novo purine and pyrimidine biosynthesis are sharply curtailed. On alkaline elution analysis, 1 hour exposure to 4 μM drug produces no single-strand breaks.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06153-02 LMCB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Clinical Pharmacology of Antineoplastic Agents and Other Drugs

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Nicholas R. Bachur	Medical Research Officer	LMCB, NCI
Others:	Pierre Dodion	Visiting Fellow	LMCB, NCI

COOPERATING UNITS *(if any)*
University of Maryland Cancer Center, (Merrill J. Egorin); University of Massachussets Medical Center, (Mary Costanza); Institute Jules Bordet, Brussels, Belgium, (Marcel Rozencweig).

LAB/BRANCH
Laboratory of Medicinal Chemistry and Biology

SECTION
Cellular Pharmacology

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In patients with cancer, the pharmacokinetics of 4'deoxydoxorubicin and its toxicity and efficacy were determined. We found the pharmacokinetic parameters highly variable, that the aldo-keto reductase product, 4'deoxydoxorubicinol, was the only detectable metabolite in plasma and urine and that other properties differed. We examined secretion of doxorubicin and cisplatin in human milk in a lactating woman with ovarian cancer. Significant amounts of doxorubicin and metabolites were secreted in the milk, but cisplatin was not detected in the milk.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06154-02 LMCB

PERIOD COVERED
October 1, 1983 to October 31, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Biochemical Pharmacology of Anticancer and Other Agents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Nicholas R. Bachur	Medical Research Officer	LMCB, NCI
Other:	Pierre Dodion	Visiting Fellow	LMCB, NCI
	Steven Averbuch	Medical Staff Fellow	LMCB, NCI

COOPERATING UNITS *(if any)*
University of Maryland Cancer Center, (Merrill J. Egorin & Su Shu Pan); Medical Center, Medical College of Georgia, (Barbara Chang); University of Colorado, Boulder, (Tad Koch).

LAB/BRANCH
Laboratory of Medicinal Chemistry and Biology

SECTION
Cellular Pharmacology

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.7	1.7	

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Since the metabolic activation of anthracycline antibiotics appears to be critical to the action and the toxicity of these agents, we have continued our investigations on the mechanisms of these activations. First, in comparison of structure activity relationships we are examining class I and class II anthracyclines. We find an increased ability of class II anthracyclines (marcellomycin and aclacinomycin) to be metabolized to nonfluorescent metabolites over class I anthracyclines (daunorubicin) by both rat liver cytosol and purified milk xanthine oxidase. We also examined in vivo metabolism of menogarol, a new anthracycline in Phase 1 trials, and found six metabolites. The major metabolite is N-demethylmenogarol. In attempts to develop means to alleviate adriamycin toxicity we are using specific chemical reagents to inactivate these drugs. Preliminary mouse experiments have yielded promising results.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06155-02 LMCB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 charactars or less. Title must fit on one line between the borders.)*
Cellular Control Mechanisms Affecting Cell Growth and Differentiation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Ronald L. Felsted	Research Chemist	LMCB, NCI
Others:	Ahmad R. Safa	Visiting Fellow	LMCB, NCI
	Constance Glover	Chemist	LMCB, NCI

COOPERATING UNITS *(if any)*
University of Maryland Cancer Center

LAB/BRANCH
Laboratory of Medicinal Chemistry and Biology

SECTION
Cellular Pharmacology

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.3	0.2	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Cell surface membrane glycoprotein structures and functions have been studied using the methods of surface labeling with I-125 of H-3 followed by two-dimensional isoelectric focusing and SDS polyacrylamide gel electrophoresis and autoradiography or fluorography. Membrane protein change during the chemical induced granulocyte differentiation of human promyelocytic leukemia HL-60 cells include the appearance of a major surface protein which is also found in normal human granulocytes and was identified as a terminal myeloid differentiation related marker. A similar analysis of a number of cytodifferentiation-inducer resistant HL-60 sublines revealed surface protein patterns in dimethylsulfoxide and 5-bromo-2'-deoxyuridine inducer resistant sublines which are very similar to wild type HL-60. In contrast, retinoic acid and 6-thioguanine resistant sublines exhibited drastic differences from wild type cells. Regardless of surface pattern, upon induction of differentiation, all cell lines revealed the same newly synthesized terminal myeloid differentiation surface protein.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06156-02 LMCB

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Pharmacodynamics of Cancer Chemotherapeutic Agents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Nicholas R. Bachur Medical Research Officer LMCB, NCI

COOPERATING UNITS *(if any)*

University of Maryland Cancer Center (Su Shu Pan & R. Gary Hollenbeck)

LAB/BRANCH

Laboratory of Medicinal Chemistry and Biology

SECTION

Cellular Pharmacology

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, MD 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.3	0.3	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We are continuing our study of catalytic activation of mitomycin C with purified enzymes. This study shows that enzymatically activated mitomycin C reacts with calf thymus DNA to yield three monofunctional adducts one of which is O6-(2'-deoxyguanosyl)-2, 7-diaminomitosene. Alkylation of DNA is very pH dependent.

Ferric ions and adriamycin in solution interact to form complexes that can yield colloidal and flocculant mixtures. At high concentrations ($Fe^{3+} > 10^{-4}$ M, adriamycin > 10^{-5} M) an absorption appears at 600 nm, indicating colloid formation, which is directly responsive to concentrations of the reactants. Evidence from dilution experiments by spectral analysis, ultracentrifugation, titration, and filtration indicate that phase transition that is sensitive to pH and time occurs with iron-adriamycin complexes to yield flocculated drug. We conclude that patients and animals treated with the iron-adriamycin preparations known as 'quelamycin' received flocculated iron-adriamycin, which accounts for the toxic and pharmacologic effects reported. It may be useful to utilize colloidal preparations of reactive or irritating drugs to avert acute toxic effects and to produce slower release of active drug.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07151-01 LMCB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Anthracycline Antibiotic Binding Proteins

PRINCIPAL INVESTIGATOR *(List other professionel personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Ronald L. Felsted	Research Chemist	LMCB, NCI
Others:	Steven D. Averbuch	Medical Staff Fellow	LMCB, NCI
	Ahmad R. Safa	Visiting Fellow	LMCB, NCI
	Constance Glover	Chemist	LMCB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Medicinal Chemistry and Biology

SECTION
Cellular Pharmacology

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.1	1.6	.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project involves the identification of specific anthracycline antibiotic macromolecular interactions in cells and the characterization of the relationship of these associations to overall drug cytotoxic and cytostatic mechanisms. The unique biological interactions will be identified by in vitro and in situ covalent labeling with radioactive photoactive anthracycline antibiotic analogues by exposure to ultraviolet light. Specific radiolabeled macromolecules will be identified and their subcellular distribution determined. Anthracycline binding proteins (ABPs) will be purified, characterized and their normal physiological functions identified. The relationship of these specific cellular associations to drug analogue uptake, efflux, subcellular localization and cytostatic activity in normal, malignant and drug resistant cells will be examined. A possible connection between ABPs and anthracycline antibiotic anti-cancer and drug resistant mechanisms will be sought.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 03580-15 LMCB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Chemical Research in the Development of New Anticancer Drugs

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	John S. Driscoll	Head, Drug Design & Chemistry Section	LMCB, NCI
Others:	Victor E. Marquez	NIH Visiting Scientist	LMCB, NCI
	Mu-Ill Lim	NCI Expert	
	Chung-Ho Kim	NIH Visiting Fellow	LMCB, NCI
	Christopher K. Tseng	NIH Visiting Fellow	LMCB, NCI
	Alberto Haces	NIH Visiting Fellow	LMCB, NCI

COOPERATING UNITS *(if any)*
Biochemistry Section, Applied Pharmacology Section, Drug Metabolism Section, LMCB

LAB/BRANCH
Laboratory of Medicinal Chemistry and Biology

SECTION
Drug Design and Chemistry Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
8.2	5.7	2.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The objective of this project is the discovery of new types of drugs which are clinically useful against cancer. The following topics are of current interest: (1) purine nucleosides as antitumor agents and transition-state inhibitors of purine nucleoside phosphorylase and analogs of Neplanocin A, (2) dinucleotide analogs of NAD as IMPD inhibitors, (3) synthesis of cytidine triphosphate synthetase inhibitors (4) synthesis of diazepinone nucleosides as antitumor agents, (5) preparation of phosphonate analogs of 2',5'-oligoadenosine trimer core and (6) synthesis of differentiating agents.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 03581-15 LMCB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Analytical Chemistry of New Anticancer Drugs

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	James A. Kelley	Research Chemist	LMCB, NCI
Others:	John S. Driscoll	Head, Drug Design & Chemistry Section	LMCB, NCI
	Philipp N. Huguenin	NIH Visiting Fellow	LMCB, NCI
	Jeri S. Roth	Chemist	LMCB, NCI

COOPERATING UNITS *(if any)*
Medicine Branch, Clinical Pharmacology Branch, Pediatric Branch, COP, DCT, NCI; Drug Interactions Section, Pharmacokinetics and Pharmacodynamics Section, LMCP; Surgical Neurology Branch, NINCDS

LAB/BRANCH
Laboratory of Medicinal Chemistry and Biology

SECTION
Drug Design and Chemistry Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, MD 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.5	1.0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The objective of this project is the research and development of analytical methods which are used to: (1) establish the structure and purity of new antitumor agents and their metabolites, (2) determine physical and chemical properties of new anticancer drugs, (3) quantitate drugs and their metabolites in biological samples to elucidate pharmacology and to determine pharmacokinetics, and (4) study reaction mechanisms of potentially useful synthetic transformations. Mass Spectrometry, gas chromatography and high-performance liquid chromatography, either alone or or in combination, are emphasized techniques. Compounds of current interest are cytidine analogs, cytidine deaminase inhibitors, oligonucleotides, nitrogen mustards, and differentiating agents. The kinetics of the acid-catalyzed isomerization of reduced pyrimidine and diazepinone ribosides has been investigated.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06152-02 LMCB

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Biochemical Toxicology of Anthracyclines; the Role of Reactive Oxyradicals

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Edward G. Mimnaugh	Chemist	LMCB, NCI
Others:	Theodore E. Gram	Supervisory Pharmacologist	LMCB, NCI
	Michael Trush	Staff Fellow	LMCB, NCI
	Birandra K. Sinha	Cancer Expert	LCP, NCI

COOPERATING UNITS *(if any)*

Department of Pharmacology, George Washington University, Washington, D.C. (Katherine Kennedy)

LAB/BRANCH

Laboratory of Medicinal Chemistry and Biology

SECTION

Drug Interactions Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	2.0	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The cardiotoxic effects of anthracyclines are well documented, and a growing body of experimental evidence has implicated reactive forms of oxygen in this life-threatening toxicity. Adriamycin and other anthracycline anticancer drugs can be enzymatically activated to semiquinone free radical intermediates which auto-oxidize to generate superoxide anion radical and other highly reactive and toxic oxygen species such as hydrogen peroxide, hydroxyl radical and singlet oxygen. These oxyradicals and activated species of oxygen can cause toxicity by attacking and damaging intracellular target molecules including nucleic acids, structural proteins, enzymes and especially, membrane unsaturated lipids. Reactive oxygen attack of membrane lipids causes extensive damage by the process of membrane lipid peroxidation, which not only disrupts the structural integrity of the membrane, but also inactivates membrane bound enzymes and produces toxic, reactive aldehyde products which can alkylate proteins and nucleic acids. Thus, anthracycline-enhanced membrane lipid peroxidation may cause damage by both direct and by secondary mechanisms. The present projects were designed to evaluate this hypothesis and to better understand the possible biochemical and molecular mechanisms which contribute to anthracycline cardiac toxicity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07119-05 LMCB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Studies on the Biochemical Toxicology of Oncolytic Platinum Compounds

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Charles L. Litterst, Pharmacologist LMCB, NCI

Other: Nahed Osman, Visiting Fellow LMCB, NCI

COOPERATING UNITS *(if any)*
Dept. Otolaryngology, Henry Ford Hospital, Detroit, MI (V. Schweitzer, M.D.);
Dept. Ob/Gyn., Univ. Louisville Med. School, Louisville, KY

LAB/BRANCH
Laboratory of Medicinal Chemistry and Biology

SECTION
Drug Interactions Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	2.5	

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Although the toxic effects of cisplatinum on kidney have been appreciated for some time, the renal handling of cisplatinum and the mechanism by which the renal toxicity occurs are still incompletely understood. These mechanisms could be more easily defined if the molecular sites of interaction of cisplatin were recognized. This project is designed to define how the kidney handles cisplatin under normal conditions and after various pretreatments or other experimental conditions. Inherent in this study is an attempt to localize the sites of interaction of cisplatin and its intracellular binding sites. This section reports the comparative effects of two different diuretic agents on platinum renal toxicity, the effect of regional arterial infusion of cisplatin on platinum levels in target tissues, the potentiation of cisplatin oto- and nephro-toxicity by concomitant administration of aminoglycoside antibiotics, and the animal pharmacokinetics of the cisplatin analog CBDCA and the differentiating agent HMBA.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07120-05 LMCB

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Role of Drug Metabolism in Modulating Toxicological Responses

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Theodore E. Gram	Pharmacologist	LMCB, NCI
Other:	Klaus Krijgsheld	Visiting Fellow	LMCB, NCI
	Michael A. Trush	Staff Fellow	LMCB, NCI
	Yoichiro Hirokata	Visiting Fellow	LMCB, NCI
	Samuel M. Tong	Visiting Fellow	LMCB, NCI
	Edward G. Mimnaugh	Chemist	LMCB, NCI
	Janet Goochee	Chemist	LMCB, NCI

COOPERATING UNITS *(if any)*

Michael C. Lowe, National Heart, Lung and Blood Institute, NIH

LAB/BRANCH

Laboratory of Medicinal Chemistry and Biology

SECTION

Drug Interactions Section

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.8	1.8	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The existence and biochemical mechanisms of organ-specific toxicity are the subject of heightened interest among toxicologists. Earlier studies in this laboratory described selective necrosis of pulmonary non-ciliated bronchiolar (Clara) cells following administration of naphthalene to mice. No damage to other lung cells was noted and no pathologic changes, as evidenced by histology or enzymic alterations, were observed. The work described in this section describes conditions under which 1,1-dichloroethylene (DCE) produces selective damage to mouse lung without morphologic or enzymatic evidence of nephro- or hepatotoxicity. Accompanying the lung damage there was a significant impairment of pulmonary cytochrome P-450 linked monooxygenase activities. Simultaneous with these changes there was a paradoxical increase in certain of these activities in kidney; these increases were found to be the result of enzyme induction.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07121-05 LMCB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Involvement of Reactive Forms of Oxygen in Drug-Induced Pulmonary Toxicity

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Michael A. Trush	Senior Staff Fellow	LMCB, NCI
Other:	Theodore E. Gram	Pharmacologist	LMCB, NCI
	Edward G. Mimnaugh	Chemist	LMCB, NCI
	Erika Ginsburg	Biologist	LMCB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Medicinal Chemistry and Biology

SECTION
Drug Interactions Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Life-threatening pulmonary toxicity as a result of anticancer drug therapy is becoming increasingly recognized. It is also becoming apparent that because of the inherent molecular properties of some antineoplastic agents, reactive oxygen may be involved in the cytotoxic reaction(s) to lung cells. The drug-induced generation of reactive forms of oxygen (superoxide anion, hydroxyl radical and singlet oxygen) can contribute to drug cytotoxicity through attack of reactive oxygen species on intracellular targets (nucleic acids, lipids, proteins) and/or through reactive oxygen-mediated activation of the drug to an active intermediate. The present projects were designed to evaluate these hypotheses in order to better understand the possible biochemical and molecular mechanisms which contribute to pulmonary toxicity elicited by antineoplastics.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07129-03 LMCB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Copper and Its Chelates in Cytotoxicity and Chemotherapy

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Marco Rabinovitz	Research Chemist	LMCB, NCI
Others:	Herbert F. Pierson	PRAT Fellow	LMCB, NCI
	Joyce M. Fisher	Chemist	LMCB, NCI
	Richard W. Fuller	Chemist	LMCB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Medicinal Chemistry and Biology

SECTION
Molecular Biology and Methods Development Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standerd unreduced type. Do not exceed the space provided.)*

Studies on the cytotoxicity and chemotherapeutic activity of copper and the copper specific ligand, 2,9-dimethyl-1,10-phenanthroline have been extended to representatives of other classes of copper binding ligands. These include diethyldithiocarbamate, ethylenebis[dithiocarbamate] and pyrithione. The copper chelates of these ligands were toxic to L1210 cells in vitro and this toxicity was correlated with their abililty to deliver copper to the cells. Treatment of mice bearing the L1210 lymphoma with copper and these ligands was limited by host toxicity, and attempts to reduce host toxicity by administration of a rescue agent, such as dimercaptopropanesulfonic acid was successful but did not improve the chemotherapeutic action. A combined treatment of copper, 2,9-dimethyl-1,10-phenanthroline and melphalan resulted in cures (70 day survivors) at a dose of melphalan which by itself was not therapeutically effective.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06140-08 LMPH

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Protein Interactions in Chromosomes; Cell Cycle and Cell Proliferation Controls

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	William Bonner	Head, Chromosome Structure and Function Section	LMPH NCI
Others:	Roy S. Wu	Cancer Expert	LMPH NCI
	Christopher Hatch	Staff Fellow	LMPH NCI
	Eric Sariban	Guest Worker	LMPH NCI
	Maurizio D'Incalci	Visiting Associate	LMPH NCI

COOPERATING UNITS *(if any)*
Department of Biological Chemistry, School of Medicine, Univ. of California, Davis; Laboratory of Biochemistry, DCBD, NCI and George Washington University Medical School.

LAB/BRANCH
Laboratory of Molecular Pharmacology, DTP, DCT, NCI

SECTION
Chromosome Structure and Function

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.0	3.75	1.25

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Using methodology developed in our group over the last several years to resolve and characterize histone variants, we have been analyzing the patterns of histone synthesis during different cell behavioral states. Histones were found to be synthesized not only during S-phase but also during G1 and the quiescent state (also termed extended G1 or G0). The qualitative pattern of histone synthesis differs between S-phase, G1 and quiescent cells, a finding which shows that the synthesis in G1 or quiescent cells is not due to contamination by S-phase cells. The histone synthesis in both G1 and quiescent cells is not linked to DNA synthesis. Histones synthesized in quiescent cells are stable and seem to be incorporated into chromatin. The results suggest that the quiescent state is not an extended G1 but a discrete state or cycle. Experiments are in progress with histone mRNA's and genes in order to elucidate this phenomenon at the gene level. Histone genes under different kinds of growth control are being isolated and characterized.

Using histone synthesis as an indicator of cell state, we are attempting to elucidate some of the mechanisms which control cell cycling and cell proliferation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 06150-03 LMPH

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)* Cell Biology Studies of Protein-associated DNA Strand Breaks Induced by DNA Intercalating Agents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Leonard A. Zwelling	Sr. Investigator	LMPH NCI
Others:	Donna Kerrigan	Chemist	LMPH NCI
	Jon Minford	Medical Staff Fellow	LMPH NCI
	Robert Glazer	Sr. Investigator	LMCB NCI
	Stanley Shackney	Sr. Investigator	CPB NCI
	Jacqueline Whang-Peng	Sr. Investigator	MB NCI
	Yves Pommier	Visiting Fellow	LMPH NCI
	Michael Mattern	Cancer Expert	LMPH NCI

COOPERATING UNITS *(if any)*

Merck Research Institute, West Point, PA (M. Bradley); LCP, DTP, NCI; MCPB, COP, NCI and the University of California, San Francisco, CA (Laurence Marton).

LAB/BRANCH

Laboratory of Molecular Pharmacology, DTP, DCT, NCI

SECTION

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2	2	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Depleting intracellular putrescine and spermidine with difluoromethylornithine enhanced the susceptibility of the cellular DNA to amsacrine-induced protein-associated DNA strand breaks. Exogenous putrescine reversed this effect.

Arabinosylcytosine, hydroxyurea and 5-azacytidine enhanced the cytotoxic and DNA breaking activities of amsacrine in murine L1210 cells. These changes appear to be mediated by alterations in the distribution of cells within the cell cycle and/or alterations in DNA methylation.

A correlation between the DNA double-strand breakage produced by amsacrine or 5-iminodaunorubicin and the cytotoxicity, mutagenicity and sister-chromatid exchange produced by the 2 intercalators was found. Single-strand scission did not correlate with these biological parameters.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 06158-01 LMPH

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

DNA Damage by 5-azadeoxycytidine in Mammalian Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Maurizio D'Incalci	Visiting Associate	LMPH NCI
Others:	Kurt W. Kohn	Lab. Chief	LMPH NCI
	Joseph Covey	Staff Fellow	LCHP NCI
	Daniel Zaharko	Lab. Chief	LCHP NCI

COOPERATING UNITS *(if any)*

Laboratory of Chemical Pharmacology, Pharmacokinetics and Pharmacodynamics Section, NCI, NIH.

LAB/BRANCH

Laboratory of Molecular Pharmacology, DTP, DCT, NCI

SECTION

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.4	0.3	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

DNA damage produced by 5-azadeoxycytidine in mouse leukemia L1210 cells was studied using the alkaline elution technique. DNA that was synthesized during the drug exposure period, and which presumably contained incorporated azacytosine residues, was found to contain alkali-labile lesions, suggestive of base-free sites. The hypothesis is being pursued that these base-free sites are a consequence of loss of azacytosine residues from the DNA, either by spontaneous decomposition or by the action of a glycosylase type of DNA repair enzyme.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06159-01 LMPH

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Studies of Potentially Crosslinkable DNA Monoadducts

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Maurizio D'Incalci	Visiting Associate	LMPH NCI
Others:	Leszek Szmigiero	Visiting Fellow	LMPH NCI
	John Hartley	Visiting Fellow	LMPH NCI
	Kurt W. Kohn	Laboratory Chief	LMPH NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Molecular Pharmacology, DTP, DCT, NCI

SECTION

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.6	0.5	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Mammalian cells are capable of repairing or inactivating DNA monoadducts of certain bifunctional drugs which are thought to kill cells by the formation of DNA crosslinks. Bifunctional drugs such as cis-Pt complexes, chloroethyl-nitrosoureas and alkylating agents form DNA crosslinks in a 2 step mechanism, involving a slow conversion of DNA monoadducts to interstrand crosslinks. This project seeks to devise a general method for the direct study of crosslinkable DNA monoadducts. A method based on the alkaline elution assay of interstrand crosslinks was devised. Using the new method, potentially crosslinkable monoadducts were demonstrated in cells treated with cis-Pt. Evidence was obtained for the repair or inactivation of crosslinkable DNA monoadducts in cells. Further work will investigate the role of this inactivation as a determinant of drug sensitivity or drug resistance.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 06160-01 LMPH

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Mechanism of Action of DNA Chloroethylating Agents and Related Alkylating Agents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Neil Gibson Visiting Fellow LMPH NCI

Others: John Hartley Visiting Fellow LMPH NCI
Kurt W. Kohn Lab. Chief LMPH NCI

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Molecular Pharmacology, DTP, DCT, NCI

SECTION

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.9	0.6

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

New chloroethylating agents are being investigated as possible replacements for anticancer chloroethylnitrosoureas (ClEtNUs). New compounds are derived which would produce less diversity of reactions than the ClEtNUs, yet retain the reactions that are essential for antitumor activity. To this end, 2-chloroethylmethylsulfonylmethanesulfonate ('ClEtSoSo', NSC 338947) is being investigated. The chemical structure of this compound suggests that it would be a more selective chloroethylating agents than ClEtNUs. Studies of human cells in culture revealed that ClEtSoSo produces the same DNA lesions as ClEtNUs, namely interstrand crosslinks, DNA-protein crosslinks and low frequencies of both DNA strand breaks and alkali-labile lesions. These lesions were assayed in human cells by alkaline elution methods. As with ClEtNUs, interstrand crosslinks by ClEtSoSo were prevented in cells rich in guanine-O6-alkyltransferase, and cell survival was enhanced. DNA alkylation products are being isolated by HPLC and will be identified by mass spectrometry in order to compare the range of DNA base adducts produced by the different chloroethylating agents.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06161-01 LMPH

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Studies of Topoisomerase II as Target of Action of Anticancer Drugs

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Kurt W. Kohn LMPH NCI

Others:
Yves Pommier LMPH NCI
Jon K. Minford LMPH NCI
Elliott Uhlenhopp LMPH NCI
Leonard A. Zwelling LMPH NCI
Michael Mattern LMPH NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH: Laboratory of Molecular Pharmacology, DTP, DCT, NCI

SECTION

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS: 4.8	PROFESSIONAL: 3.8	OTHER: 1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The effects of DNA intercalating agents and epipodophyllotoxins are being studied. These drugs produce protein-associated DNA strand breaks in mammalian cells and isolated nuclei. The activity responsible for this effect was isolated from cell nuclei and was identified as topoisomerase II. The drugs tend to trap DNA-topoisomerase II complexes in a state in which the enzyme is covalently linked to DNA. This effect is stimulated by the intercalating agents: amsacrine (m-AMSA), 5-iminodaunorubicin, 9-hydroxy-2-methylellipticinium, ellipticine and adriamycin; and by the epipodophyllotoxins: etoposide and teniposide. The methylellipticinium derivative also inhibits this reaction at high concentrations. All of the drugs inhibit the ATP-dependent strand-passage reaction of the enzyme. The genomic localization and regulatory functions of topoisomerase II are under study.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06117-12 LTCB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Molecular and Physiological Control Mechanisms in Normal and Neoplastic Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Robert C. Gallo	Chief	LTCB NCI
Prem S. Sarin	Chemist	LTCB NCI
W. Carl Saxinger	Microbiologist	LTCB NCI
Flossie Wong-Staal	Microbiologist	LTCB NCI
John Horneff	Clinical Associate	LTCB NCI
Martha Michalski	Clinical Associate	LTCB NCI
Lee Ratner	Clinical Associate	LTCB NCI
Leonard Seigel	Clinical Associate	LTCB NCI

COOPERATING UNITS *(if any)*
Stu Aaronson, Viral Carcinogenesis Branch, National Cancer Institute; Rolf Neth, University of Hamburg; Robin Weiss, Imperial Cancer Research Fund, London, England; Dani Bolognesi and Bart Haynes, Duke University; Ken McCredie, M. D.

LAB/BRANCH
Laboratory of Tumor Cell Biology

SECTION Sections on Hematopoietic Cellular Control Mechanisms, Hematopoietic Cell Biochemistry and Immunology, and Molecular Genetics of Hematopoietic Cells.

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
51	28	23

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This Laboratory is concerned with five areas of research: (1) molecular and physiological control mechanisms in normal and neoplastic cells, designed to obtain information on the molecular mechanisms involved in neoplastic transformation, including a search for and cloning of viral genomes and genome products in human tumor tissues; (2) the identification, isolation and demonstration of biological activity of viral information in human leukemic cells and cells from patients with acquired immune deficiency syndrome (AIDS); (3) search for biochemical markers of minimal neoplastic disease and the development of practically useful microtests for the detection of such markers; (4) cell differentiation in vitro. (This relates to a major interest of the Laboratory: Does the phenotypic abnormality of leukemia in man result from a block in leukocyte maturation?) (5) Based on new information in the literature and from studies within this laboratory, new approaches to cancer chemotherapy are evaluated in in vitro and in vivo systems. This is the ultimate goal of the Laboratory.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 7148-01 LTCB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Cellular Biological Studies on T-Cell Malignancies and Lymphomas

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Prem S. Sarin	Chemist	LTCB NCI
Martha Michalski	Clinical Associate	LTCB NCI
S. Zaki Salahuddin	Cancer Expert	LTCB NCI
Beatrice Macchi	Visiting Associate	LTCB NCI
Mikulas Popovic	Visiting Associate	LTCB NCI
Jorg Jendis	Visiting Fellow	LTCB NCI
Yoshitaka Taguchi	Visiting Fellow	LTCB NCI
Carla Grandori	Guest Worker	LTCB NCI

COOPERATING UNITS *(if any)*
Robin Weiss, Imperial Cancer Research Fund, London, England; Bart Haynes, Duke University; Ken McCredie, Anderson Hospital and Tumor Institute; Umberto Torelli, University of Modena; Luc Montagnier, Pasteur Institute, Paris; Kendall Smith,

LAB/BRANCH
Laboratory of Tumor Cell Biology

SECTION
Hematopoietic Cellular Control Mechanisms

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
14	8	6

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The cell biology studies have identified a number of HTLV-I isolates from patients with adult T-cell leukemia-lymphoma (ATLL), lymphosarcoma cell leukemia from different parts of the world including Japan, the Caribbean, and southeastern United States. These HTLV-I isolates have been transmitted to T-cells from cord blood cells, peripheral blood and bone marrow. The T-cells infected with HTLV are transformed and have convoluted nuclei, a characteristic similar to the one observed in the patients' tumor cells. HTLV-I has been isolated from family members of a Japanese patient with ATLL. These virus isolates have properties similar to those isolated from the ATLL patient. The HTLV-I infected cells produce a number of lymphokines. The lymphokines that have been identified include MIF (migration inhibitory factor) which inhibits the migration of fresh human macrophages), MAF (macrophage activating factor), DIF (differentiation inducing factor), CSF (colony stimulating factor), EOS-GMA (eosinophil growth and maturation activity), FAF (fibroblast activating factor) and γ-interferon. All these lymphokines were detected in unconcentrated tissue culture fluids from most of the HTLV-I positive T cell lines. HTLV-I infected cell lines produce these lymphokines constitutively and are an excellent source for these factors. A variant of HTLV-I was isolated from a patient with hairy cell leukemia (HTLV-II) and more recently from a patient with AIDS. HTLV-II has properties similar to HTLV-I and can infect and transform cord blood cells more efficiently than peripheral blood or bone marrow cells. More recently another HTLV variant (HTLV-III) has been isolated from a number of patients with AIDS and pre-AIDS. HTLV-III is cytopathic like HTLV-I and HTLV-II, but it does not cross-react with monoclonal antibody produced against HTLV-I p19. HTLV-III has been transmitted into a T-cell line which is productively infected. With the availability of this cell line it should be possible to produce large quantities of the virus to study biological and biochemical properties. In addition, studies are in progress to determine if HTLVI, HTLVII and HTLV-III can induce leukemia (lymphoma) or AIDS in subhuman primates.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 7149-01 LTCB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Molecular Biological Studies on HTLV and Oncogenes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Flossie Wong-Staal	Microbiologist	LTCB NCI
John Horneff	Clinical Associate	LTCB NCI
Lee Ratner	Clinical Associate	LTCB NCI
Suresh Arya	Cancer Expert	LTCB NCI
Marvin Reitz	Cancer Expert	LTCB NCI
Eric Westin	Cancer Expert	LTCB NCI
Genoveffa Franchini	Visiting Associate	LTCB NCI
Anna Aldovini	Visiting Fellow	LTCB NCI

COOPERATING UNITS *(if any)*
Stu Aaronson, Viral Carcinogenesis Branch, National Cancer Institute; Rolf Neth, University of Hamburg; Robin Weiss, Imperial Cancer Research Fund, London, England; Dani Bolognesi and Bart Haynes, Duke University; Ken McCredie, M.D.

LAB/BRANCH
Laboratory of Tumor Cell Biology

SECTION
Molecular Genetics of Hematopoietic Cells

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
18	12	6

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Studies on human retroviruses and oncogenes have been pursued with particular emphasis on their role in human disease. Two subgroups of a human T-cell leukemia virus, designated as HTLV-I and HTLV-II, have the unique capacity to transform human T-cells in vitro, leading to clonal cell populations. Molecular cloning and comparative analyses of the genomes of HTLV-I and HTLV-II, revealed sequence conservation throughout, but particularly in a coding region designated pX and in an enhancer sequence in the viral LTR. These results have direct relevance in the possible mechanism of transformation by these viruses. In addition, variants of HTLV-I with transforming capabilities have been analyzed. Recently, a T-lymphotropic retrovirus (HTLV-III) found in most patients with this disorder has been postulated to be the etiologic agent of the acquired immunodeficiency syndrome (AIDS). Analyses of HTLV-III genome indicate that this virus is related to HTLV-I and -II. A mRNA c-sis oncogene has been cloned from HTLV positive cells (HUT-102). This cDNA clone is 2.8 Kb and appears to include the entire v-sis homologous region and all of the coding sequences. The construction, which includes the SV40 promotor and transcriptional regulatory signals, morphologically transforms NIH 3T3 cells and the transformed cells are highly malignant in nude mice. The DNA sequence of the HUT-102 c-sis is similar to that of normal cells, indicating that the normal c-sis gene contains all the information necessary for malignant transformation. The small envelope protein (p21e) gene of HTLV has been incorporated into a vector which includes a mouse metallothionine promotor and this gene is expressed in mouse fibroblasts. The relationship of HTLV to the expression of extra HLA class I antigens by HTLV-I infected cells has been studied. Using molecular clones of HLA genes and of HTLV it has been observed that sequences coding for the extracellular portion of the class I heavy chain hybridize under conditions which would detect distantly related sequences specific to the pX region of HTLV-I. Studies to put the HTLV pX gene into a mammalian expression vector are in progress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 7150-01 LTCB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Seroepidemiological Studies on Human T-Lymphotropic Retroviruses

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

W. Carl Saxinger	Microbiologist	LTCB NCI
Marjorie Robert-Guroff	Staff Fellow	LTCB NCI
Jorg Schupbach	Visiting Fellow	LTCB NCI

COOPERATING UNITS *(if any)*
Dani Bolognesi, Duke University; Yohei Ito, University of Kyoto; Bill Haseltine, Harvard University; Volker Erfle, Munich; Bill Blattner, Environmental Epidemiology Section, NCI; Mark Smulson, Georgetown University; Isaac Witz, Tel Aviv.

LAB/BRANCH
Laboratory of Tumor Cell Biology

SECTION
Hematopoietic Cell Biochemistry and Immunology

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
6	3	3

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The worldwide distribution of HTLV infection, the mechanisms of its transmission and its role in various types of T-cell malignancies and patients with acquired immune deficiency syndrome (AIDS) and pre-AIDS has been extensively studied. A highly sensitive enzyme linked immunosorbent assay (ELISA) has been developed to detect HTLV antibodies in sera from different donors. Using the techniques of ELISA and competition radioimmunoassays, it has been shown that: (1) HTLV-I infection is associated primarily with adult T-cell leukemia-lymphoma (ATLL). The ATLL patients frequently have lymphadenopathy, skin involvement and hypercalcemia. (2) Relatives of ATLL positive patients in the HTLV endemic areas were approximately four times more susceptible to possess HTLV antibodies than unrelated healthy donors. (3) Seroepidemiologic studies in Jamaica show a high prevalence of HTLV-I antibodies in patients with non-Hodgkins lymphoma, and chronic lymphocytic leukemia of the B-cell type. (4) In Venezuela, HTLV-I antibodies were detected (1-14%) in different regions. High HTLV antibody incidence was correlated with areas endemic for anthropod borne diseases. (5) A study of Surinam immigrants to the Netherlands show that 12% of these immigrants who are drug users have HTLV-I antibodies, whereas control Dutch drug users do not have any HTLV antibodies. (6) Studies on patients with AIDS and pre-AIDS show that approximately 85% of these patients have HTLV-III antibodies, whereas only around 10% of these patients were found to be positive for HTLV-I antibodies. (7) High levels of HTLV-I antibody were detected in African population in Ghana, Nigeria, Uganda, and South Africa. (8) Transmission studies involving baboons with malignant lymphoma from an experimental colony in Sukhumi have shown facile HTLV transmission to other baboons, macaques and owl monkeys as evidenced by seroconversion. (9) Low levels of HTLV-I antibodies have been detected in sera of Danish patients with Sezary syndrome and mycosis fungoides. (10) Monoclonal antibodies against a 52,000 dalton glycoprotein of HTLV-I have been developed. The specific antigen recognized is located on the surfaces of HTLV transformed cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06308-13 BRB

PERIOD COVERED
October 1, 1983 through September 30, 1984

TITLE OF PROJECT *(60 characters or less. Title must fit on one line between the borders.)*
Biometric Research Branch

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Richard M. Simon, Chief, Biometric Research Branch, CTEP, DCT, NCI
Others:
Susan S. Ellenberg, Biometric Research Branch, CTEP, DCT, NCI

COOPERATING UNITS *(if any)* Developmental Therapeutics Program, DCT, NCI; Radiation Research Program, DCT, NCI; Biological Response Modifiers Program, DCT, NCI; Clinical Oncology Program, DCT, NCI.

LAB/BRANCH
Biometric Research Branch

SECTION

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	2.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Biometric Research Branch (BRB) is the statistical component for planning, scientific monitoring and assessment of the national and international research program of the Division of Cancer Treatment. The branch provides statistical leadership for all extramural activities of the division. The branch is also responsible for statistical consultation and collaboration with the research activities of the Biological Response Modifier Program, Developmental Therapeutics Program, and Radiation Research Program and performs collaborative research with components of the Clinical Oncology Program.

The Biometric Research Branch performs statistical planning and evaluation of all NCI supported therapeutic clinical trials. The branch performs scientific monitoring for the statistical aspects of the conduct and analysis of trials performed via cooperative agreement or contract. Primary statistical direction is provided by the branch for the conduct of selected national and international studies of therapeutic interventions, prognostic factors, pre-clinical screening and diagnostic imaging. The branch performs evaluations of therapeutic interventions based upon syntheses of results from multiple studies.

The Biometric Research Branch conducts research on experimental designs, biometric methods and biomathematical approaches for the development and efficient evaluation of improved cancer treatments.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 07200-02 CO

PERIOD COVERED

October 1, 1983 - September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cellular Immunity Against Human T-cell Leukemia/Lymphoma Vi s (HTLV)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Samuel Broder, M.D., Associate Director, Clinical Oncology Program, DCT, NCI

COOPERATING UNITS *(if any)*

Laboratory of Tumor Cell Biology, DCT, NCI
Laboratory of Human Carcinogenesis, DCCP, NCI

LAB/BRANCH

Office of the Associate Director, Clinical Oncology Program

SECTION

INSTITUTE AND LOCATION

National Cancer Institute, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2	2	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The term HTLV (human T-cell leukemia/lymphoma virus) denotes an extended family of retroviruses discovered and characterized in the DCT Laboratory of Tumor Cell Biology under the supervision of Dr. Robert Gallo. There are currently three known members of this family (HTLV-I, HTLV-II, and HTLV-III), and it is quite likely that more members will be discovered in the future. The first two members have been linked to human neoplasms, and HTLV-I (the virus about which the most is known) has been linked to the pathogenesis of adult T-cell leukemia. The most recently discovered member of the HTLV family (HTLV-III) is thought to be the etiologic agent of acquired immunodeficiency syndrome (AIDS), and it has several immunologic and biochemical features in common with the other viruses.

Very little is known about how infection and integration of HTLV into the genome will affect the immune function of T cells that themselves have reactivity for the virus. The purpose of the current project was to characterize the functional consequences of HTLV-infection in HTLV-specific T cells using the first member of the family (HTLV-I) as a prototype. The results indicate that HTLV-I can transform clones with a helper/inducer phenotype as well as clones with a suppressor/cytotoxic phenotype. This transformation can be associated with a progressive loss of T-cell function or a cytopathic effect on the target cell under the appropriate circumstances.

The human type-C retrovirus known as human T-cell leukemia virus (HTLV-I) was first isolated from neoplastic cells derived from black patients in the United

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07201-01 CO

PERIOD COVERED
October 1, 1983 - September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
HTLV-I and Altered Immune Function

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Samuel Broder, Associate Director, Clinical Oncology Program, NCI
Dr. Hiroaki Mitsuya, Expert, Clinical Oncology Program, NCI
Dr. Marvin Reitz, Senior Investigator, Laboratory of Tumor Cell Biology, NCI
Dr. Robert Gallo, Chief, Laboratory of Tumor Cell Biology, NCI

COOPERATING UNITS *(if any)*
Laboratory of Tumor Cell Biology, DCT, NCI

LAB/BRANCH
Office of the Associate Director, Clinical Oncology Program, DCT, NCI

SECTION

INSTITUTE AND LOCATION
National Cancer Institute, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2	2	0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The term HTLV (human T-cell leukemia/lymphoma virus) denotes an extended family of retroviruses discovered and characterized in the DCT Laboratory of Tumor Cell Biology under the supervision of Dr. Robert Gallo. There are currently three known members of this family (HTLV-I, HTLV-II, and HTLV-III). The most recently discovered member of the HTLV family (HTLV-III) is thought to be the etiologic agent of acquired immunodeficiency syndrome (AIDS), and it has several immunologic and biochemical features in common with the other viruses.

While it is well known that some HTLV viruses can infect and transform T cells, the functional changes that occur in normal T cells that are specifically reactive for a common soluble antigen (for example, tetanus toxoid) are not known. The purpose of the current project was to characterize the functional consequences of HTLV infection in normal human T-cell clones with specificity for soluble tetanus toxoid (and purified protein derivative) using the first and most extensively studied member of the family (HTLV-I) as a prototype. The results indicate that HTLV-I can transform antigen-specific T cells. One unprecedented consequence of HTLV infection in such cells is the loss of the normal T-cell requirement for accessory cell presentation in the activation of an *in vitro* proliferative response to soluble antigen. Such infected T-cell clones appear capable of binding soluble antigen directly - and colonies of such immune - but infected T-cell clones specifically contract upon exposure to antigen.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 07202-01 BDMS

PERIOD COVERED
October 1, 1983 through September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Biostatistics and Data Management Section

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	Robert W. Makuch	Head	BDMS, COP, DCT, NCI
Others:	Robert W. Wesley	Senior Investigator	BDMS, COP, DCT, NCI
	Margaret N. Wesley	Senior Staff Fellow	BDMS, COP, DCT, NCI

COOPERATING UNITS *(if any)*
Cancer Therapy Evaluation Program, DCT, NCI.

LAB/BRANCH

SECTION
Biostatistics and Data Management Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Section is the statistical and data management component of the Clinical Oncology Program (COP), and provides statistical leadership and data management consultation for major activities of the Program. The Section is involved in the design, conduct, monitoring, and statistical analyses of intramural and national multicenter clinical trials of experimental treatments for cancer. Other major collaborative efforts include studies to identify important prognostic and treatment selection factors, evaluate diagnostic procedures, develop improved staging systems, and investigate tumor resistance to chemotherapy using mathematical models. The Section develops new statistical designs and biometric methods related to the development and evaluation of new cancer treatments. The Section maintains computerized data collection systems for intramural and national multicenter clinical protocols. The Section works closely with interested branches to improve data recording and retrieval and provides other services, such as extraction of information from PDQ. The Section provides liaison with the Clinical Center Medical Information System team and the Clinical Center Pharmacy, allowing COP input into decisions which directly impact patient care and protocol management. The Section assists the Deputy Clinical Director to insure adequate monitoring of protocols through the MIS Toxicity and Protocol Monitoring screens and other mechanisms.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-CM-06513-08-CP

PERIOD COVERED: October 1, 1983, to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Molecular Pharmacology of Antitumor Agents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Bruce A. Chabner, M.D., Director, DCT — DCT, NCI
Gregory A. Curt, M.D., Special Asst. for Clin. Affairs, OD, DCT — DCT, NCI
Carmen J. Allegra, M.D., Clinical Associate — CPB, DCT, NCI
Brenda D. Bailey, M.D., Staff Fellow — CPB, DCT, NCI
Desmond Carney, M.D., Visiting Scientist — NCI-Navy Med. Oncol. Br., DCT, NCI
Kenneth H. Cowan, M.D., Ph.D., Senior Investigator — CPB, DCT, NCI

[continued on next page]

COOPERATING UNITS *(if any)*: NCI-Navy Medical Oncology Branch

LAB/BRANCH: Clinical Pharmacology Branch

SECTION: Office of the Chief

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
7.5	5.5	2.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

During the past year we have continued to examine the role of polyglutamate forms of methotrexate (MTX) in the cytotoxic action of this drug. We have completed studies describing the formation, retention, and binding of polyglutamates in human breast cancer cells. These findings were summarized in last year's report. In new projects, we have undertaken a detailed analysis of the inhibitory effect of MTX polyglutamates on a number of enzymes involved in the synthesis of DNA precursors. We have found that MTX is a weak, uncompetitive inhibitor of thymidylate synthetase (TS), while the polyglutamates are much more potent noncompetitive inhibitors of the same enzyme, with K_is 2 to 3 logs lower than the parent compound. In addition we have found that MTX polyglutamates inhibit the rate of formation of complex between FdUMP folate and TS, but have no effect on the dissociation rate of this complex. The competition for complex formation appears to be noncompetitive in nature. The analysis of binding studies with TS indicates that the MTX polyglutamates could have potent direct inhibitory effect on TS independent of the depletion of folate pools caused by DHFR inhibition. We have pursued the concept of additional sites of action of polyglutamates, examining enzymes involved in purine synthesis and folate interconversions. This work has established that the MTX polyglutamates potently inhibit AICAR and GAR transformylases, in contrast to the weak or nonexistent inhibition by the parent compound. We have developed a method for highly purifying AICAR transformylase by affinity chromatography, and intend to characterize the catalytic mechanism of this enzyme more fully. Enhanced inhibition by polyglutamates at this site is consistent with the notion that the competitive nature of leucovorin rescue may be the result of competition of reduced folates with the MTX polyglutamates for inhibited enzymes such as AICAR transformylase. In addition, we have examined several folate interconverting enzymes and have found enhanced inhibition of 5-10-methylene-

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-CM-06515-05-CP

PERIOD COVERED
October 1, 1983 - September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Biochemistry of the Adriamycin-Iron Complexes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Charles E. Myers, M.D.,	Chief	CPB, COP, DCT, NCI
Josephia Muindi, M.D., Ph.D.	Visiting Fellow	CPB, COP, DCT, NCI
Birandra Sinha, M.D.	Cancer Expert	CPB, COP, DCT, NCI
Miriam Sohn, Ph.D.	Sr. Staff Fellow	CPB, COP, DCT, NCI
Helen Eliot	Biologist	CPB, COP, DCT, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Pharmacology Branch

SECTION
Biochemical Pharmacology Section

INSTITUTE AND LOCATION
NIH, National Cancer Institute, Bethesda, MD 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.5	3.5	1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In previous years, we had reported on the ability of adriamycin to complex iron and engage in redoxactivity. This past year, we have extended these observations in a number of ways.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-CM-06516-03-CP

PERIOD COVERED
October 1, 1983 - September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Drug Resistance in Human Tumor Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Kenneth H. Cowan, M.D., Ph.D.,	Sr. Staff Fellow	CPB, COP, DCT, NCI
Merrill E. Goldsmith, Ph.D.	Staff Fellow	CPB, COP, DCT, NCI
Elizabeth Rubacalba, B.A.,	Chemist	CPB, COP, DCT, NCI
Marie Ricciardone, M.S.,	Chemist	CPB, COP, DCT, NCI
Carolyn Beckman,	Student Volunteer	CPB, COP, DCT, NCI

COOPERATING UNITS *(if any)*
Medicine Branch, COP, DCT, NCI
Pediatric Oncology Branch, COP, DCT, NCI

LAB/BRANCH
Clinical Pharmacology Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NCI, National Institutes of Health, Betnesda, MD 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4	2	2

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Our laboratory is working in the area of drug resistance in human tumor cells. We have recently described a methotrexate resistant human breast cancer cell line (MTX^R MCF-7) which contains amplified dihydrofolate reductase genes as the mechanism of resistance. We have now cloned the human genomic dihydrofolate reductase gene from this cell line as well as two non functional human DHFR pseudogene. We have also constructed a functional dihydrofolate reductase minigene using both genomic and cDNA sequences. This dihydrofolate reductase minigene has been transfected into mutant chinese hamster cells which are deficient in DHFR activity. The human DHFR minigene is able to rescue these mutant cells within a relatively high frequency (.12%). In addition, we are developing various deletion mutants of this gene in order to identify those DNA sequences which are necessary for functional expression as well the sequences which are necessary for the intracellular modulation of DHFR gene expression. Because the efficiency of transfection of this minigene is quite high in the absence of many additional viral DNA sequences added to it, we are now studying whether the human dihydrofolate reductase gene contains any DNA sequences which function as enhancer sequences. We have also studied the regulation DHFR gene expression in human breast cancer lines. These studies have shown that estrogen increases while tamoxifin decreases the expression of the DHFR gene at the level of transcription. Other studies have confirmed that methotrexate (MTX) also induces DHFR levels and the mechansism this regulation is currently under investigation. We have also a developed another methotrexate resistant human breast cancer cell line in our lab with multiple defects associated with drug resistant. In collaboration with Dr. Jacques Jolivet we have shown that this methotrexate cell line (MTX^R ZR-75) has multiple defects including

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-CM-06518-03-CP

PERIOD COVERED: Oct. 1, 1983 to Sept. 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Pharmacokinetics

PRINCIPAL INVESTIGATOR *(List other professionel personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Jerry M. Collins, Ph.D.	Pharmacologist	CPB, COP, DCT, NCI
Raymond Klecker, B.S.	Chemist	CPB, COP, DCT, NCI
John Strong, Ph.D	Pharmacologist	CPB, COP, DCT, NCI
Charles Myers, M.D.	Branch Chief	CPB, COP, DCT, NCI
Jean Jenkins, R.N.	Research Nurse	CPB, COP, DCT, NCI
Gregory Curt, M.D.	Oncologist	CPB, COP, DCT, NCI
Gerald Batist, M.D.	Oncologist	CPB, COP, DCT, NCI
Solomon Zimm, M.D.	Oncologist	PB, COP, DCT, NCI

COOPERATING UNITS *(if any)*

NCI/DCT: MB, SB, PB, ROB, LMCP
Non-NCI: BEIB/DRS/NIH; SNB/NINCDS/NIH
University of Maryland Cancer Center

LAB/BRANCH: Clinical Pharmacology Branch

SECTION: Pharmacokinetics Section

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, MD 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.0	5.0	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The primary function of this group has been to apply the principles of pharmacokinetics to questions of relevance to the treatment of cancer. Studies completed or active include:

1. Regional drug delivery, including intraarterial, intraperitoneal, and intraventricular routes of administration -- Pediatric, Surgery, and Surgical Neurology Branches.
2. Halogenated pyrimidine radiosensitizers -- Radiation Oncology Branch
3. Phase I trials of new agents (Tiazofuran, Dihydroazacytidene, Carboplatinum, Spiromustine) -- Medicine and Surgical Neuorology Branches
4. Pharmacokinetic evaluation of established agents -- Adriamycin, 6-mercaptopurine, cisplatin -- Medicine and Pediatric Branches

In addition to direct clinical pharmacokinetic projects, this group has ongoing projects on the relationship between preclinical and human pharmacokinetic studies. Both experimental studies (rodents) and theoretical aspects are included. Similarly, this group is interested in the relationships between in vitro chemosensitivity and in vivo response.

More detailed pharmacokinetic modeling has been jointly developed in collaboration with the Biomedical Engineering and Instrumentation Branch, DRS/NIH.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-CM-06519-01-CP

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Non-Invasive Studies of Metabolism Using Nuclear Magnetic Resonance Methods

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Jack S. Cohen, Ph.D.	Research Chemist	CPB, COP, DCT, NCI
Chi-Wan Chen, Ph.D.	Staff Fellow	CPB, COP, DCT, NCI
Richard Knop, M.D., Ph.D.	NMR Expert	DR, CC
Desmond Carney, M.D.	Sr. Staff Fellow	MB, COP, DCT, NCI
James Mitchell, M.D.	Cancer Expert	ROB, COP, DCT, NCI
Angelo Russo, M.D.	Staff Fellow	ROB, COP, DCT, NCI
Gil Navon, Ph.D.	Visiting Scientist	Tel Aviv Univ., Israel
Robbe Lyon, Ph.D.	Staff Fellow	CPB, COP, DCT, NCI
Adrian Bax, Ph.D.	Staff Fellow	LCP, NIADDK

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Pharmacology Branch

SECTION
Biophysical Pharmacology Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, MD 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A true understanding of cellular biology, and of therapeutic effects on pathological conditions under a variety of experimental conditions, requires the noninvasive monitoring of metabolism. Nuclear magnetic resonance (NMR) methods enable metabolism to be studied noninvasively. We have developed a cell perfusion technique allowing the effective application of NMR methods to cell lines grown in culture. This technique consists of embedding cells in a neutral agarose gel thread (0.5 mm) which allows continuous perfusion and rapid diffusion of metabolites into the cells. The method is applicable to any cells, including anchorage-independent cells, and to any NMR spectrometer. We are currently applying ^{31}P, ^{1}H and ^{13}C NMR to study the metabolism of normal and cancerous cells and the effects of perturbants, such as heat and drugs, upon them. We are also developing sensitive surface coils using the same multi-nuclear NMR approach. This will enable us to carry out investigations on rodents in vivo, in order to correlate findings with the well-controlled in vitro studies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-CP-06520-01-CP

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Magnetic Resonance Imaging Applied to Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Jack S. Cohen, Ph.D.	Research Chemist	CPB, COP, DCT, NCI
Nicholas Patronas, M.D.	Radiologist	DR, CC
Richard Knop, M.D.	NMR Expert	DR, CC
Miriam Sohn, Ph.D.	Sr. Staff Fellow	CPB, COP, DCT, NCI
Charles E. Myers, M.D.	Chief	CPB, COP, DCT, NCI
Chi-Wan Chen, Ph.D.	Staff Fellow	CPB, COP, DCT, NCI
David Colcher, M.D.	Chemist	DCBD, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Pharmacology Branch

SECTION
Biophysical Pharmacology Branch

INSTITUTE AND LOCATION
NIH, National Cancer Institute, Bethesda, MD 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

To develop strategies to facilitate the application of magnetic resonance imaging (MRI) to the detection of malignant growths. Specifically to develop contrast agents to enhance the vizualization of tumors. These agents are considered to be valuable both for the increase in intrinsic contrast relative to surrounding soft tissue, as well as the discrimination between benign and malignant growths by MRI. Also, by the use of MRI to attempt to localize the in vivo distribution of anti-cancer drugs.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-CM-06521-01-CP

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Conformations and Interactions of Nucleic Acids, Proteins and Drugs in Solution

PRINCIPAL INVESTIGATOR *(List other professionel personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Jack S. Cohen, Ph.D.	Research Chemist,	CPB, COP, DCT, NCI
Chi-Wan Chen, Ph.D.	Staff Fellow,	CPB, COP, DCT, NCI
C.H. Niu, Ph.D.	Staff Fellow	LPC, NIADDK
Richard Knop, M.D., Ph.D.	Expert	DR, CC
Babul Borah, Ph.D.	Vis. Assoc.	CPB, COP, DCT, NCI
Charles E. Myers, M.D.	Chief	CPB, COP, DCT, NCI

COOPERATING UNITS *(if any)*
Laboratory of Chemical Physics, NIADDK (for spectrometer maintenance)

LAB/BRANCH
Clinical Pharmacology Branch

SECTION
Biophysical Pharmacology Section

INSTITUTE AND LOCATION
NIH, National Cancer Institute, Bethesda, MD 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Details of the interactions of biological macromolecules (proteins and nucleic acids) in solution with each other and with small effector molecules, such as hormones and drugs, are being probed at the molecular level. Generally such interactions are mediated by conformational alterations in the macromolecule. The method of choice to investigate the conformations of proteins and nucleic acids in solution is nuclear magnetic reasonance (NMR) spectroscopy. We have used ^{1}H, ^{2}H, ^{13}C and ^{31}P NMR in combination with selective stable isotopic enrichment (^{2}H and ^{13}C) to study the conformations and solution properties of proteins and DNA. Currently we are focusing on the effects of base sequence on the conformational transitions of polydoxynucleotides and the effects of cytotoxic drugs on those transitions. We are applying 2-dimensional proton NMR to obtain relative atomic distances and hence are able to define DNA conformations and effects of drug complexation in solution in molecular detail.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-CM-06522-01-CP

PERIOD COVERED: October 1, 1983 to September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Enzymatic Mechanisms Protecting Cells Against Free Radical Damage

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Charles E. Myers, M.D.	Chief	CPB, COP, DCT, NCI
Aspandiar Katki, Ph.D.,	Guest Researcher	CPB, COP, DCT, NCI
Gupreet Dhillon, Ph.D.,	Guest Researcher	CPB, COP, DCT, NCI
Gerald Batist, M.D.,	Visiting Associate	CPB, COP, DCT, NCI
Kenneth Cowan, M.D., Ph.D.	Sr. Staff Fellow	CPB, COP, DCT, NCI

COOPERATING UNITS *(if any)*

Victor Ferrans, M.D., Chief of Ultrastructure, NHLRI
Jean Herman, FDA

LAB/BRANCH

Clinical Pharmacology Branch

SECTION

Biochemical Pharmacology Section

INSTITUTE AND LOCATION

NIH, National Cancer Institute, Bethesda, MD 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.25	1.625	2.125

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

During the past year, the activity of this group has increased dramatically. This is the result of several years spent building a technical base that is now coming to fruition. In general, the focus of this group is to describe how mammalian cells get rid of hydrogen peroxide and other oxygen radicals. Most of the work has concerned glutathione peroxidase. This enzyme is a selenium dependent enzyme which has been very well studied in animals but about which little is known in man. We became interested when experimental evidence showed that selenium effected the toxicity of adriamycin. Our interest was further stimulated by the growing evidence that selenium modulates the action of several carcinogens and may be an important anticarcinogen in man. This has been rendered more understandable by the recent evidence that oxygen radicals such as superoxide and hydroxyl radical as well as peroxide are critical in both carcinogenesis and promotion. With this background in mind, we have been following a broad based research plan to delineate the relevant biochemistry in man and animals.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 03403-19 M

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Clinical Trials and Miscellaneous Clinical Investigations

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Robert C. Young	Chief	M	NCI
Other:	Bruce Chabner	Director	DCT	NCI
	Charles Myers	Chief	CP	NCI
	Richard Fisher	Sr Investigator	M	NCI
	Marc Lippman	Sr Investigator	M	NCI
	Edward Gelmann	Sr Staff Fellow	M	NCI
	Dan Longo	Sr Investigator	M	NCI

COOPERATING UNITS *(if any)*: Radiation Oncology Branch, NCI; Navy-MOB, NCI; Clinical Pharmacology Branch NCI; Biometric Research Branch,NCI; Surgery Branch,NCI; Immunology Branch, NCI; Laboratory of Molecular Pharmacology, Environmental Epidemiology Branch, NCI.

LAB/BRANCH: Medicine Branch

SECTION:

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
30	21.5	8.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Medicine Branch is a major clinical facility of the NCI. Its activities are divided between clinical therapeutic trials in cancer patients and related laboratory research. Clinical trials of cancer treatment are currently underway in breast cancer, ovarian cancer, Hodgkin's disease, non-Hodgkin's lymphomas, testicular tumors, Kaposi's sarcoma in AIDS, soft tissue sarcomas, cervical carcinoma, and melanoma. Phase I-II clinical trials have been completed this year on the following new experimental agents: CBDCA, AZQ, Interferon. Phase II trials continue on CBDCA, AZQ, interferon, and intraperitoneal chemotherapy of aclacinomycin. Phase I studies include dihydro-5-azacytidine (DHAC), tiazofuran and trimetrexate. Additional summaries of clinical studies are summarized under reports entitled "Clinical Program in Breast Carcinoma." Laboratory research of the Branch is summarized under reports entitled, "Mechanisms of Drug Resistance, Cytogenetic Studies, Immunologic Aspects of Malignant Lymphomas, Mechanisms of Hormone Dependence of Human Malignancy, Genetic Regulation of the Immune Response, and Retroviruses and Transforming Genes in Malignancy.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 03404-13 M

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Immunologic Aspects of Malignant Lymphomas

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Richard Fisher	Sr Investigator	M	NCI
Other:	Susan Bates	Clinical Associate	M	NCI
	Narendra Tuteja	Visiting Fellow	M	NCI
	Frieda Bostick-Bruton	Technician	M	NCI
	Toby Hecht	Cancer Expert	M	NCI
	Dan Longo	Sr Investigator	M	NCI
	Elaine Jaffe	Sr Investigator	LP	NCI

COOPERATING UNITS *(if any)*: Laboratory of Immunoregulation, NIAID; Laboratory of Pathology, DCBD, NCI

LAB/BRANCH: Medicine Branch

SECTION:

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.5	3.5	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the spece provided.)*

Ongoing studies are attempting to determine the origin and immunologic function of Reed-Sternberg cells in Hodgkin's disease by characterizing a neoplastic cell line obtained from a patient with advanced Hodgkin's disease. Initial studies demonstrated that the L-428 cell line is a potent stimulator of the human primary mixed lymphocyte response. The time course, dose response characteristics, nature of the responding cell, and the ability of the response to be blocked by monoclonal anti-I-A antibodies are all characteristic of mixed lymphocyte reactions. Of interest, the MLC response occurs without detectable interleukin I production in the cultures. This cell line is also capable of serving as an accessory cell for proliferative responses of purified T cells to mitogens. Purified T cells from patients with advanced stages of Hodgkin's disease have reduced proliferation in the presence of the L-428 accessory cell consistent with an inherent T cell deficit in patients with Hodgkin's disease. Studies have been initiated to determine the ability of the L-428 cells to present soluble antigens to T cell clones in a genetically restricted fashion. In regard to immunologic function and cell surface characteristics, the L-428 tumor cells resemble the dendritic cell.

Mouse monoclonal antibodies have been prepared against the L-428 tumor cell and react with Reed-Sternberg cells in tissue sections obtained from patients. The specificity of these monoclonal antibodies is now being determined. The characterization of the antigen being recognized by the monoclonal antibodies is in progress.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06119-15 M

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 charecters or less. Title must fit on one line between the borders.)*
Cytogenetic Studies

PRINCIPAL INVESTIGATOR *(List other professionel personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Jacqueline Whang-Peng,	Senior Investigator	MB	NCI
Other:	Turid Knutsen	Med Tech.	MB	NCI
	Elaine Lee	Med Tech.	MB	NCI
	Chein-Song Kao-Shan	Visiting Assoc.	MB	NCI
	John Minna	Branch Chief	MOB-NNMC	NCI
	Paul Bunn	Sr. Investigator	MOB-NNMC	NCI
	Kenneth Cowan	Sr. Staff Fellow	CPB	NCI

COOPERATING UNITS *(if any)*
Pediatric Oncology Br., NCI; Clinical Pharm. Br., NCI; Clin. Hematol. Br., NHLBI; Medical Oncol. Br - NNMC, NCI; Lab. Chem. Biol, NIADDK; Radiat. Oncol., Br., NCI; Louisiana State University; Div. Virol, Bureau Biologics, FDA

LAB/BRANCH
Medicine Branch

SECTION
Cytogenetic Oncology

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5	3	2

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The areas of investigation:

1. Cytogenetic studies of human neoplastic, hematological, and congenital disease, with special emphasis on patients with aquired immune deficiency syndrome (AIDS) who develop leukemia, lymphoma, or Kaposi's sarcoma, and patients with adult T-cell lymphoma and leukemia.

2. In situ hybridization studies:

   a. Localization of c-oncogenes (c-myc, c-sis, c-fms, etc.) in the neoplastic cells (direct or tissue culture) of Burkitt's lymphoma (including /AIDs), CML, Ewing's sarcoma, 5q-syndrome, etc.

   b. Localization of genes for β, ε and γ hemoglobin and insulin, H-ras, and c-myc in normal and two variants of the CML tissue culture line K562.

   c. Localization of HTLV gene in patients with HTLV positive diseases; one patient with HTLV leukemia has been studied thus far.

   d. Localization of the genes for DHFR in various HSR and double minute bearing tissue culture lines.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06700-11

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Clinical Program in Breast Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Marc E. Lippman	Senior Investigator	M	NCI
Other:	Caroline Bagley	Nurse	M	NCI
	Margaret Wesley	Biostatistician	BR	NCI
	Peggie Findlay	Physician	ROB	NCI
	Sandra Levy	Senior Investigator	DCCR	NCI
	Helene Smith	Collaborator	Peralta	CA

COOPERATING UNITS *(if any)*

Biometric Research Branch, NCI; Radiation Oncology Branch, NCI; Surgery Branch, NCI, Peralta Cancer Research Institue, CA.

LAB/BRANCH: Medicine Branch and Division of Cancer Control and Rehabilitation

SECTION: Medical Breast Cancer Section

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3 1/2	2 1/2	1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Medical Breast Cancer Section is responsible for the development of a clinical and laboratory program directed at breast cancer. Clinical trials in metastatic disease comparing chemotherapeutic, hormonal and chemohormonal regimens are underway. Biochemical and hormonal receptor studies are undertaken and coordinated by the Medical Breast Cancer Section. Clinical studies consist of a major chemotherapy trial aimed at stimulating human breast cancer cells with hormonal agents for more successful cell cycle phase specific chemotherapy; a hormonal therapy trial aimed at prospectively evaluating the usefulness of steroid receptors for estrogens, androgens and progestins in human breast cancer. Concurrent cytokinetic data are being collected. An advanced disease hormonal therapy trial comparing tamoxifen plus fluoxymesterone to tamoxifen plus danazol, and a Phase II trial of CBDCA. We have developed a successful treatment program for Stage III-Stage IV Mo breast cancer (objective response rate 33/35). We are attempting to further refine these techniques. We have initiated a randomized trial to explore the usefulness of an in vitro chemosensitivity assay system in collaboration with Helene Smith, Ph.D. (Peralta Cancer Research Institute). A trial for Stage IV no evidence of disease patients has been initiated. In addition there is an endocrine and chemotherapy program for male breast cancer. A cooperative trial between the Surgery, Radiation and Medicine Branches is underway comparing excisional biopsy plus definitive radiotherapy to simple mastectomy in clinical Stage I and II breast cancer. All patients have axillary dissections; A-C chemotherapy is given to all N+ patients; 150 patients are on study.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06702-09 M

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Mechanisms of Hormone Dependence of Human Malignancy

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Marc E. Lippman	Senior Investigator	M	NCI
Other:	Attan Kasid	Visiting Associate	M	NCI
	Diane Bronzert	Technician	M	NCI
	Karen Huff	Technician	M	NCI
	Susan Aitken	Technician	M	NCI
	Robert Dickson	Senior Staff Fellow	M	NCI
	Nancy Davidson	Medical Staff Fellow	M	NCI
	Dwight Kaufman	Medical Staff Fellow	M	NCI

COOPERATING UNITS *(if any)*: Laboratory of Biochemistry, NCI

LAB/BRANCH: Medicine Branch

SECTION: Medical Breast Cancer Section

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
10	10	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A. We are studying the molecular mechanisms by which estrogens specifically alter growth of human breast cancer.

1. We have introduced viral onc genes (ras and myc) into human breast cancer cells. These retroviruses are stably integrated and viral mRNA is expressed at high levels. Effects on cell phenotype are under investigation.

2. We are using the technique of differential hybridization to identify specific estrogen regulated genes for cloning and subsequent analysis.

3. We have identified and partially purified several estrogen induced growth factors which are secreted by breast cancer cells into the medium. Some of the activities cross react with EGF receptor and are candidate novel transforming growth factors. Others cross react in IGF-1 type assays.

4. We have successfully prepared monoclonal antibodies to the secreted proteins of human breast cancer cells. One is an antibody against one of the growth factors. These antibodies and their antigens are being characterized and their biological activity is being assessed in vitro and in nude mice.

5. We have examined the regulation of thymidine kinase on estrogen regulated enzyme, activity by using a cDNA for human thymidine kinase.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06708-05 M

PERIOD COVERED: October 1, 1982 to September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Genetic Regulation of the Immune Response

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Louis A. Matis	Senior Staff Fellow	M	NCI
	Dan L. Longo	Senior Investigator	M	NCI
Other:	Ada Kruisbeek	Cancer Expert	M	NCI
	Barry L. Gause	Clinical Associate	M	NCI
	Ronald Steis	Clinical Associate	M	NCI
	Tai-Chi Shan	Guest Researcher	M	NCI
	Margaret Weston	Biologist	M	NCI
	Danny Dean	Biologist	M	NCI

COOPERATING UNITS *(if any)*

Immunology Branch, NCI
Laboratory of Immunology, NIAID

LAB/BRANCH: Medicine Branch

SECTION: Experimental Immunology Section

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☒ (b) Human tissues
- ☐ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

1. The mechanism of thymic determination of MHC restriction of T lymphocytic antigen recognition.

2. Extrathymic influences on the T cell repertoire.

3. T Cell influence on immunoglobulin class-switch by B cells.

4. HTLV transformation of B lymphocytes.

5. Clonal analysis of the immune response to a murine retrovirus-associated lymphoma.

6. Examination of the T lymphocyte repertoire by generation of T cell clones from radiation-induced bone marrow chimeras.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06709-04 M

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Mechanisms of Drug Resistance

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Robert F. Ozols	Sr. Investigator	M	NCI
Other:	Robert C. Young	Chief	M	NCI
	Karen Grotzinger	Med Technologist	M	NCI
	Wilma McCoy	Med Technologist	M	NCI
	Thomas C. Hamilton	Staff Fellow	M	NCI
	Brent Behrens	Medical Staff Fellow	M	NCI
	Karen Louie	Medical Staff Fellow	M	NCI

COOPERATING UNITS *(if any)*

Laboratory of Medicinal Chemistry and Pharmacology
Clinical Pharmacology Branch

LAB/BRANCH: Medicine Branch

SECTION:

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5	4	1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We are studying the biology of ovarian cancer and the mechanisms of antineoplastic drug resistance in human tumors. This has required the development of human ovarian cancer cell lines in tissue culture and in nude mice xenografts. The dose response curves to antineoplastic drugs are generated using a clonogenic assay. Cell lines from previously untreated patients which are sensitive in vitro have been incubated with progressively increasing concentrations of melphalan, adriamycin and cisplatin to produce drug resistant variants. With these sets of cell lines [endogenously resistant, endogenously sensitive, and their resistant variants] we are examining the mechanisms of drug resistance at a cellular level and biochemical manipulations which can restore sensitivity in the resistant cell lines.

We have characterized 3 new ovarian cancer cell lines including a line which has steroid hormone receptors. We have also developed drug resistant variants which are 6-10 times more resistant than the primary cultures. We have also developed a new transplantable intraperitoneal model of human ovarian cancer in nude mice which produces ascites, pulmonary metastases and death from intraabdominal carcinomatosis. We have demonstrated that melphalan resistance is linked to glutathione levels. Furthermore, using techniques to alter the levels of glutathione or to change the permeability of cell membranes, we have been able to restore drug sensitivity in melphalan and adriamycin resistant cell lines, respectively. These experimental studies have led to a clinical trial of verapamil plus adriamycin in refractory ovarian cancer patients.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06710-02 M

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Retroviruses and Transforming Genes in Malignancy

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Edward Gelmann Senior Investigator M NCI

COOPERATING UNITS *(if any)*

Pediatrics Branch, COP, DCT, NCI

LAB/BRANCH: Medicine Branch

SECTION: Medical Breast Cancer Section

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4	4	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A. We are studying chromosomal translocation and onc genes in Burkitt's lymphoma. We have cloned and sequenced the t(8:14) chromosome translocation from a Burkitt's lymphoma cell line (ref. 1). This line contains a translocated and rearranged myc onc gene. We have now directed our attention to a Burkitt's lymphoma cell line with a t(8:22) translocation wherein myc is neither rearranged, translocated, nor activated. We are characterizing the structure of the translocation in this line and investigating the possible involvement of other onc genes.

B. Human cytomegalovirus (HCMV) is highly associated with AIDS and Kaposi's sarcoma. We have been studying nucleic acid homology between the myc onc gene and a genomic fragment of HCMV that is able to transform cells in culture after DNA-mediated gene transfer. We are also characterizing Kaposi's cell lines and tissue for the expression of this transforming viral genomic fragment.

C. The estrogen-responsive MCF-7 human breast cancer cell line has been shown experimentally to alter its growth performance and malignant potential in response to exogenous hormonal stimulation. It also appears that in response to estrogen stimulation these cells secrete a number of growth promoting proteins. We are in the process of cloning mRNA sequences expressed in response to estrogen stimulation of MCF-7 cells.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 03024-15 NMOB

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Clinical Trials and Other Clinical Investigations

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Daniel C. Ihde, M.D., Chief, Clinical Investigations Section, NCI-NMOB

COOPERATING UNITS *(if any)*

See attached sheets

LAB/BRANCH

NCI-Navy Medical Oncology Branch

SECTION

Clinical Investigations Section

INSTITUTE AND LOCATION

Naval Hospital, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
56	16	40

CHECK APPROPRIATE BOX(ES)

- [X] (a) Human subjects
  - [ ] (a1) Minors
  - [ ] (a2) Interviews
- [X] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The NCI-Navy Medical Oncology Branch studies new methods of evaluating and treating patients with malignant disease and provides general medical oncology consultations for the Naval Hospital Bethesda. Clinical investigations are carried out in patients with small cell lung cancer and other types of lung cancer (epidermoid, large cell, and adenocarcinoma), mycosis fungoides and the Sezary syndrome, lymphomas, breast and testicular cancer, and multiple myeloma and other plasma cell dyscrasias. New Phase I and Phase II agents, both chemotherapeutic and immunotherapeutic, are studied. Other interests involve general medical oncology and miscellaneous cancers. Within each disease category, investigations are centered in one or more of the following areas: 1) therapeutic trials and complications of treatment; 2) staging procedures, prognostic factors, and natural history; 3) clinical cell biologic correlations; 4) review articles. Some 30 oncology consultations per month are seen in the NHBETH and outpatient care (200 visits/week) provided for patients requiring chemotherapy who are not eligible for any protocol studies.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 06575-09 NMOB

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Laboratory Investigation of Tumor Cell Biology

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

NCI-Navy MOB Senior Staff

John D. Minna, M.D.	Chief	(USPHS)
Adi F. Gazdar, M.D.	Deputy Chief (Lab)	
Paul A. Bunn, M.D.	Senior Investigator	
Mary J. Matthews, M.D.	Senior Investigator	
Desmond N. Carney, M.D.	Senior Investigator	
James L. Mulshine, M.D.	Senior Investigator	

COOPERATING UNITS *(if any)*

See attached sheet

LAB/BRANCH

NCI-Navy Medical Oncology Branch

SECTION

Human Tumor Cell Biology Laboratory

INSTITUTE AND LOCATION

Naval Hospital Bethesda, Bethesda, MD 20814

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
17.5	8	9.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project uses a multidisciplinary approach to study tumor cell biology so as to understand the basic nature of human malignancy and to develop methods for the diagnosis and control of human cancer. Particular emphasis is placed on lung cancer and cutaneous T-cell lymphomas. Our major efforts are in the growth of human tumors in vitro and in the nude mouse to study the differentiation, cell kinetics, immunology, experimental therapy, biochemistry, growth factor requirements, tumor markers, and ectopic hormone secretion in these model systems. The human tumor colony forming and nude mouse xenograft assays are used to study tumor biology and to test tumor sensitivity in vitro. Another major area is the use of somatic cell hybrids and DNA transfection to study tumor cell biology, genetics and drug-radiation resistance. These include production of monoclonal antibodies by hybridomas against tumor antigens and defined proteins, comparative gene mapping, human hormone production, and genes controlling expression of the malignant phenotype. Other areas studied include tumor cell kinetics, flow cytometric analysis of human tumors, and DNA content of tumor samples.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06576-01 NMOB

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Laboratory Studies of the Biology of Malignant T Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Dr. P. A. Bunn, Jr.
Dr. C. F. Winkler
Dr. E. Boven, Fogarty Fellow
Dr. T. Lindmo, Fogarty Fellow
P. Jewitt, Technical Staff

COOPERATING UNITS *(if any)*

Drs. R.C. Gallo and F. Wong-Staal (Laboratory of Tumor Cell Biology), NCI
Dr. S. Broder (Laboratory of the Director), COP, NCI
Dr. J. Whang-Peng (Cytogenetics Section, Medicine Branch), NCI

LAB/BRANCH

NCI-Navy Medical Oncology Branch

SECTION

Laboratory of Cellular Kinetics

INSTITUTE AND LOCATION

NIH/NCI/DCT/COP/NCI-NMOB

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.5	3	2

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The goals of these studies have been to establish and characterize malignant T cell lines, to optimize the methods for serum free growth of normal and malignant T cell lines, to define growth factors and growth factor receptors for these lines, to examine other lymphokines produced by these lines and to determine the effects of monoclonal antibodies, monoclonal antibody conjugates, biologicals and chemotherapeutic agents on these lines.

We have established a new HTLV(+) permanent T Cell line, Hut 516, which has been in permanent culture for greater than 2 years. The line produces a number of lymphokines listed below. We have defined a serum free BITES medium which supports the growth of this and other T cell lines as well as serum supplemented medium.

We have characterized a new monoclonal antibody, anti-HV, which binds to the TCGF receptor. However, the epitope of the receptor to which it binds does not block binding of TCGF or anti-tac. The antibody may be useful in the diagnosis and treatment of HTLV associated adult T cell lymphomas (ATL). It may also be useful in studies of the TCGF receptor especially after treatment with anti-Tac.

In concert with our clinical serotherapy trials we have established methods for evaluating the immunoreactivity of monoclonal antibodies conjugated with drugs, toxins or radionuclides. We have shown that ^{125}I conjugated antibodies (T101, 9.2.27) are capable of selective cell killing (up to 3 logs) of malignant cells in vitro. We have developed an in vitro model for these studies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06577-01 NMOB

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Laboratory Studies of Cellular Kinetics of Human Malignancies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Dr. P. A. Bunn NCI-NMOB NCI

COOPERATING UNITS *(if any)*

M. Lippman, M.D. (Medicine Branch) NCI

LAB/BRANCH

NCI-Navy Medical Oncology Branch

SECTION

Cellular Kinetics Section

INSTITUTE AND LOCATION

Naval Hospital, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2	2	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have shown the role for measurement of DNA content in a variety of tumors including lung cancer, myeloma, and T Cell lymphomas. The studies will continue.

We have shown that a number of monoclonal antibodies are cell cycle related (e.g., anti-HV, anti-Tac) while others are not (e.g., 1IG11, 534F8, KC4).

Collaborative laboratory studies associated with the breast cancer, lung cancer, and lymphoma protocols measuring cell cycle parameters, DNA content, and monoclonal antibody binding are continuing.

We plan to assess drug sensitivity testing using an automated system with the cell sorter during the next year. Drug sensitivity testing in the malignant lymphomas will also be instituted in the next year.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06578-01-NMOB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Structure, Expression of Peptide Hormone Genes in Human Small Cell Lung Carcinoma

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: J. Battey NCI-NMOB
E. Sausville NCI-NMOB

COOPERATING UNITS *(if any)*

LAB/BRANCH
NCI-Navy Medical Oncology Branch

SECTION
Laboratory of Genetics, Molecular Biology and Immunology

INSTITUTE AND LOCATION
NCI, DCT, COP, Bethesda, Maryland 20814

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	2	1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Many human small cell lung carcinomas make peptide hormones in the patient and in tissue culture cell lines derived from biopsy specimens. Two of these peptide hormones, arginine vasopressin (AVP) and bombesin/gastrin releasing peptide (GRP) appear to stimulate lung cancer cell growth under certain culture conditions. Other recent advances in oncogene research have shown that some oncogenes may be related to growth factors or their receptors. C-sis encodes a product with areas of homology to PDGF, and similarly the presumed product of erb-B may be related to the EGF receptor. To understand better the mechanism and importance of peptide hormone expression in small cell lung cancer cells, we are studying the structure and function of peptide hormone polyprotein genes and analyzing their expression in small cell tissue culture lines.

We have obtained genomic clones of human AVP and oxytocin (OT) genes and determined their structure and nucleotide sequence. RNA blot analysis and S1 nuclease protection experiments have documented the mRNA initiation sites and probable promoter region for three forms of the mRNA transcribed in this cell. In addition, we have obtained a human genomic clone for the pro-opiomelanocortin (POMC) polyprotein gene which encodes the peptide hormones ACTH, MSH, and lipotropin. Several small cell lung cancer lines produce POMC mRNA, and we are presently characterizing the structure of this transcription unit and comparing it to the normal mRNA made in the anterior pituitary.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06579-01-NMOB

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Translocations that Highlight Chromosomal Regions of Differentiated Activity

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: I. R. Kirsch NCI-NMOB
G. F. Hollis NCI-NMOB

COOPERATING UNITS *(if any)*

LAB/BRANCH: NCI-Navy Medical Oncology Branch

SECTION: Laboratory of Genetics, Molecular Biology & Immunology

INSTITUTE AND LOCATION: NCI, DCT, COP, Bethesda, Maryland 20814

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2	2	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standerd unreduced type. Do not exceed the space provided.)*

Background: Burkitt lymphoma, a tumor of B lymphocyte, immunoglobulin producing, cells is associated with specific chromosomal breakpoints in the precise regions where the immunoglobulin gene loci, kappa, lambda, and heavy chain reside. Our analyses of the Burkitt lymphoma-system over the past few years led us to consider the possibility that what we were observing in this tumor vis a vis its specific translocations might be generalized to the issue of all chromosomal translocations. Given the involvement of the immunoglobulin gene encoding regions in the translocations associated with this immunoglobulin producing tumor we asked whether translocations seen in cells of other differentiated function frequently involved the regions to which genes responsible for that differentiated function resided.

Analyses: An obvious choice to start this study were globin producing erythroleukemias because of the general availability of globin DNA probes to use for the analysis, and because production of globin was such a clearly differentiated function of these cells. In collaboration with cytogeneticists and hematopathologists at the Medical College of Virginia we have karyotyped two patients with newly diagnosed erythroleukemia and found a number of karyotypic abnormalities including chromosomal aberrations of the globin encoding regions (patient 1, t(7; 11); (patient 2, t(16;17)) in the tumor cells but not normal fibroblasts from both these patients. Our hypothesis is not that erythroleukemia is necessarily caused by a translocation into the globin encoding regions. We feel, however, that in cells that have activated or are in the process of activating their globin loci, the chromosomal regions to which these loci map will have an increased susceptibility to undergo karyotypic aberration compared to quiescent areas of the genome.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06580-01-NMOB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Developmentally specific expression of oncogenes in Erythroid cells

PRINCIPAL INVESTIGATOR *(List other professionel personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	Gregory F. Hollis	NCI-NMOB
	Ilan R. Kirsch	" "

COOPERATING UNITS *(if any)*

LAB/BRANCH
NCI-Navy Medical Oncology Branch

SECTION
Laboratory of Genetics, Molecular Biology & Immunology

INSTITUTE AND LOCATION
Naval Hospital, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2	2	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects
☐ (a1) Minors
☐ (a2) Interviews
☒ (b) Human tissues
cell lines
☐ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Background: Malignantly transformed cells can be viewed as cells frozen in a specific stage of differentiation. Recent studies, by many laboratories, have implicated qualitative or quantitative changes in the expression of a class of genes, referred to as oncogenes, as playing an important role in establishing and maintaining the transformed state. To understand how a change in expression of these genes is related to transformation a more detailed knowledge of the normal expression and function of these genes must be obtained. For instance, to determine if oncogene expression plays a role in determining the phenotype of a cell, it is important to know whether the expression of a particular oncogene is linked to the stage of differentiation of the cell.

Results: We have chosen to examine the relationship between specific oncogene expression and the state of differentiation by studying the expression of oncogenes at different stages of erythroid development in the mouse. To do this, we have screened Friend induced murine erythroleukemia cells for the coincident expression of non-Friend related oncogenes. The oncogenes analyzed, myb, myc, erb A, erb B and ets have all been cited as contributing to the transformed state of erythroid cells in avian systems. Only myc and myb showed significant transcription in this system being seen in both Friend virus alone and Friend complex (Friend helper plus spleen focus-forming virus, SFFV) induced erythroleukemias.

GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06581-01 NMOB

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Molecular Genetics of B-Lymphocyte Development and Transformation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: W. Michael Kuehl, Senior Investigator NMOB, NCI

Others: Richard Currie Staff Associate " "
Timothy P. Bender Staff Associate " "
Shoshanna Segal Cancer Expert " "

COOPERATING UNITS *(if any)*

Laboratory of Microbiol Immunology, NIAID, H. C. Morse); LCMB, NCI (J. Pierce, S. Aaronson); NMOB, NCI (G. Hollis, I. Kirsch); MB, NCI (D.L. Longo).

LAB/BRANCH: NCI-Navy Medical Oncology Branch

SECTION: Genetics, Molecular Biology and Immunology

INSTITUTE AND LOCATION: NCI, NIH, NNMC, Rockville Pike, Bethesda, MD

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.6	3.6	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues cell lines ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A. Overall objectives:
1. To clarify the cellular and molecular bases for regulation of immunoglobulin gene expression
2. To clarify the cellular and molecular bases for B lymphocyte development
3. To identify B cell line models representing different stages of B cell development which can differentiate or dedifferentiate in appropriate in vivo or in vitro microenvironments
4. To clarify the relationships between B lymphocyte transformation and B-lymphocyte development

B. Species studied: mice and humans

C. Specific Studies:
1. Identification of B-lymphocyte stage-specific transforming genes (with J. Pierce and S. Aaronson)

Transfection of S107 mouse myeloma DNA into NIH-3T3 cells resulted in tentative identification of an "activated" K-ras cellular oncogene but no stage specific transforming gene (SSTG) as defined by the criteria established by G. Cooper and colleagues (e.g., Cell 28, 873-880, 1982 and Nature 302, 114-119, 1983). We also obtained the human B-lym clone from G. Cooper in an attempt to confirm his results and as a potential positive control for identifying SSTG in the NIH-3T3 transfection assay. Despite using a number of NIH3T3 sublines and various transfection protocols, we were unable to identify morphologically distinct transformed Loci using the cloned human B lym gene. By cotransforming this gene with the selectable pSV2gpt plasmid, preliminary studies show that all 10 cotransformed NIH3T3 cells clones examined contain multiple (ca 5-50 copies) of the human B lym

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06811-02 PB

PERIOD COVERED
October 1, 1983, to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Controlled Trial of Adjuvant Chemotherapy in the Treatment of Osteosarcoma

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Angela Miser	Visiting Fellow	PB, NCI
Others:	P. Pizzo	Chief	PB, NCI
	S. Rosenberg	Chief	SB, NCI
	A. Baker	Senior Investigator	SB, NCI

COOPERATING UNITS *(if any)*
Pediatric Oncology Group, Gainesville, FL (M. Link)

LAB/BRANCH
Pediatric Branch

SECTION

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	0.0

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Treatment of localized osteosarcoma with amputation alone has historically resulted in long-term relapse-free survival of approximately 20%, although recently relapse-free survival of greater than 40% has been reported in surgically-treated patients. Although several chemotherapeutic agents have been found to cause tumor stabilization or regression in patients with overt tumor, their benefit in the adjuvant setting following surgical removal of all identifiable tumor is much debated. The objective of this multi-institutional study is to evaluate the efficacy of adjuvant chemotherapy using the currently available front-line drugs in children with localized extremity osteosarcoma. Following either amputation or limb salvage procedure, patients are randomized to receive either a 43-week course of chemotherapy using bleomycin/actinomycin D/cyclophosphamide, high-dose methotrexate, adriamycin and cis-platinum (regimen 1), or no immediate chemotherapy (regimen 2). Patients being observed on regimen 2 will receive chemotherapy only in the event of overt tumor recurrence, following attempt at surgical resection of all recurrent tumor. Both time to first relapse and ultimate survival are being evaluated.

Since May 1982, approximately 35 patients have been randomized on this study (16 from NCI) of whom 29 have been evaluated in the most recently available Pediatric Oncology Group report. Although there is at least a trend towards superiority of the chemotherapy arm in time to first relapse, detailed review is being performed before full statistical analysis is completed. There is at present no difference in ultimate survival between the two arms.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06813-02 PB

PERIOD COVERED
October 1, 1983, to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Molecular Biology of Pediatric Tumors

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Mark A. Israel	Head, Molecular Genetics Section	PB, NCI
Others:	J. Bolen	Senior Staff Fellow	PB, NCI
	C. Thiele	Senior Staff Fellow	PB, NCI
	N. Rosen	Medical Staff Fellow	NMOB, NCI
	J. Miser	Cancer Expert	PB, NCI
	T. Triche	Head, Ultrastructural Pathology	LP, NCI
	J. Whang-Peng	Head, Cytogenetic Oncology Section	MB, NCI

COOPERATING UNITS *(if any)*
Dept. of Microbiology, Columbia Univ. (C. Prives); Dept. of Microbiology, State Univ. of N.Y., Stonybrook (J. Brugge); Naval Medical Res. Inst., Bethesda (P. Reynolds).

LAB/BRANCH
Pediatric Branch

SECTION
Molecular Genetics Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5	4	1

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Our laboratory program has continued to pursue investigations directed at understanding the molecular mechanisms underlying transformation and tumorigenesis induced by polyoma virus, while expanding our investigation of the molecular basis of several important questions in pediatric oncology. Experiments focused on the study of oncogenic transformation induced by polyoma virus include: 1) Characterization of a complex between the polyoma virus transforming gene product, middle T antigen, and the cellular proto-oncogene, c-src, in polyoma infected and polyoma transformed cells; 2) Demonstration of a significant increase in the specific activity of c-src tyrosyl kinase activity in the species of c-src which is physically associated with polyoma middle T antigen in cells transformed by polyoma virus; 3) Demonstration of enhanced c-src tyrosyl kinase activity specifically mediated by polyoma middle T antigen prior to the physical association of c-src with polyoma middle T antigen; 4) Development of an *in vitro* assay in which the association of polyoma middle T antigen with c-src can be evaluated; 5) Identification of the c-src kinase activity as the major tyrosyl phosphotransferase in immunoprecipitates of polyoma middle T antigen.

Studies directed at better understanding the molecular events important for the malignant characteristics of pediatric tumors include: 1) Characterization of the biologic and cytogenetic features of cell lines established from pediatric solid tumors; 2) Molecular biological evaluation of cell lines from neuroepithelioma and Ewing's sarcoma to elucidate the biologic significance of the rcp(11;22) translocation in these cells; 3) Evaluation of the effect of retinoic acid induced differentiation on the expression of genes important for the malignant phenotype of cell lines from patients with Stage IV neuroblastoma; 4) Development of lines of investigation which will be useful in identifying genes whose function may be biologically significant for the malignant behavior of pediatric neoplasia.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06814-02 PB

PERIOD COVERED
October 1, 1983, to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Biology and Treatment of Pediatric Soft Tissue and Ewing's Sarcomas

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	James S. Miser	Expert	PB, NCI
Others:	P. Pizzo	Chief	PB, NCI
	E. Glatstein	Chief	ROB, NCI
	T. Kinsella	Senior Investigator	ROB, NCI
	J. Mulvihill	Chief	CEB, NCI
	M. Israel	Head, Molecular Genetics Sect.	PB, NCI
	T. Triche	Head, Ultrastructural Path. Sect.	LP, NCI
	D. Longo	Head, Experimental Immunol. Sect.	MB, NCI

COOPERATING UNITS *(if any)*
Rehabilitation Medicine, CC (L. Gerber)

LAB/BRANCH
Pediatric Branch

SECTION

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The study of pediatric sarcomas including Ewing's sarcoma, rhabdomyosarcoma, and undifferentiated sarcomas, as well as other sarcomas, is being undertaken in two areas: biological studies and therapeutic trials.

The biological studies address: 1) in vitro tissue culture evaluation and characterization of the cell lines from tumors of patients with these sarcomas; 2) in vitro differentiation of cell lines derived from tumors of patients with these sarcomas; 3) development of monoclonal antibodies to pediatric sarcomas; 4) definition of the cytogenetics of pediatric sarcomas; and 5) in vitro radiation and chemosensitivity of cell lines derived from tumors of patients with these sarcomas. The cytogenetic characterization of Ewing's sarcoma, peripheral neuroepithelioma has confirmed the translocation τ (11;22) in all cell lines studied with these disorders.

The therapeutic studies address: 1) improvement in therapy for patients with high risk pediatric sarcomas a) by improving the initial induction rate using an intensive induction and b) by utilizing intensive consolidation including high dose chemotherapy, total body radiotherapy, and autologous bone marrow reinfusion; 2) improvement in therapy for patients with moderate risk pediatric sarcomas; 3) improvement in the detection, evaluation, and treatment of pulmonary metastasis in patients with pediatric sarcomas; 4) careful evaluation of the short and long term effects of chemotherapy and total body radiotherapy on cardiac and pulmonary function, as well as other major organ systems; 5) evaluation of the efficacy and toxicity of autologous bone marrow transplantation in the treatment of pediatric sarcomas using a new chemotherapeutic and radiotherapeutic regimen.

Since the 83-C-73 protocol was begun in early 1983 over 45 patients have been entered. For newly diagnosed patients the initial complete remission rate has been greater than 85% and greater than 70% remain in remission. These figures represent improvement over previous regimens utilized at this institution.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 06815-02 PB

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(60 characters or less. Title must fit on one line between the borders.)*

The Investigation and Treatment of Patients with Non-Hodgkin's Lymphoma

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Ian T. Magrath	Senior Investigator	PB, NCI
Other:	Philip A. Pizzo	Chief	PB, NCI
	David G. Poplack	Head, Leukemia Biology Section	PB, NCI
	Mark A. Israel	Head, Molecular Genetics Section	PB, NCI
	James A. Miser	Cancer Expert	PB, NCI

COOPERATING UNITS *(if any)*

Clinical Chemistry, Clinical Center

LAB/BRANCH

Pediatric Branch

SECTION

INSTITUTE AND LOCATION

National Cancer Institute, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
10	8	2

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Eighty-five patients have now been admitted to the primary protocol for the treatment of non-Hodgkin's lymphoma, and the goals of this protocol, namely, to define different prognostic groups within this broad category of patients have largely been achieved. Utilizing a CHOP - high dose methotrexate regimen, the results in lymphoblastic lymphoma without marrow involvement and patients with entirely resected intraabdominal undifferentiated lymphoma or localized disease have been excellent (currently 82% and 90% disease-free survival). Among the remaining patients the most important prognostic feature is bone marrow involvement. These findings have been utilized in the design of protocols in which treatment is tailored to prognostic groups.

Overall, the results of the present protocol show a 15% improvement in terms of disease-free survival over the two previous protocols used in the Pediatric Branch, when the previous results are combined (justified on the basis of a previous multi-institutional study which showed no difference in outcome between these protocols). The results of 77-04-02 which includes IT therapy also appear to be improved compared to results prior to the introduction of CNS prophylactic IT therapy.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06816-01 PB

PERIOD COVERED
October 17, 1983, to September 30, 1984

TITLE OF PROJECT *(80 charecters or less. Title must fit on one line between the borders.)*
Studies of the Nature, Measurement and Management of Pain in Children with Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	A. Miser	Visiting Fellow	PB, NCI
Others:	P. Pizzo	Chief; Head, Infect. Dis. Sec.	PB, NCI
	J. Miser	Expert	PB, NCI
	A. Chang	Senior Investigator	SB, NCI
	C. Restrepo	Expert	LP, NCI
	R. Wesley	Senior Staff	BR, NCI

COOPERATING UNITS *(if any)*
Pharmacy Dept., CC (R. Greene); Neurology and Anesth. Br., NIDR (R. Gracely); Developmental Human Genetics Branch, NICHD (A. Mukherjee); Dept. of Rehab., CC (J. Hicks, M. Lampert, C. McGarvey); (continued next page)

LAB/BRANCH
Pediatric Branch

SECTION

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	2.5	

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Research involving children with cancer experiencing pain is centered in three areas: clinical evaluation, descriptive studies, and therapy.

For clinical evaluation, 3 different modalities of pain measurement viz. a visual analog scale, a verbal descriptor scale, and a picture scale are being compared to evaluate their feasibility of administration and reliability in children of all ages experiencing acute or chronic pain.

Descriptive studies consist of (1) The prospective study of the predictive factors and nature of phantom limb pain and sensations in patients undergoing amputation and (2) The study of the prevalence and nature of pain in a childhood cancer population at initial presentation.

Therapeutic studies in progress are:-(1) Study of the efficacy and kinetics of a continuous intravenous or subcutaneous infusion of morphine sulfate in patients with malignancy who are experiencing pain, in which the pharmacokinetics of morphine and changes in blood β endorphin level are being studied in children requiring widely differing morphine doses to control severe pain; morphine kinetic data is also being obtained in a primate model, (2) Study of the use of nitrous oxide for children with malignancy undergoing painful procedures.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06830-14 PB

PERIOD COVERED
October 1, 1983 - September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Infectious Complications of Malignancy: Diagnosis, Management and Prevention

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Philip A. Pizzo	Head, Infectious Disease Section; Chief	PB, NCI
Other:	D. Cotton	Senior Staff Fellow	PB, NCI
	J. Hathorn	Clinical Associate	PB, NCI
	M. Browne	Clinical Associate	PB, NCI
	I. Ioannou	Visiting Fellow	PB, NCI

Continued on next page

COOPERATING UNITS *(if any)*
Medicine Branch, NCI; Surgery Branch, NCI; Diagnostic Microbiology, CC; USUHS; WRAIR; U. Penn; Johns Hopkins; Clinical Section, NIDR

LAB/BRANCH
Pediatric Branch

SECTION
Infectious Disease

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.5	4.5	1.0

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Our studies are devoted to developing methods to define patients at high risk for infection, improving the ability to diagnose infections early, treat them effectively and ultimately prevent them.

We are seeking to differentiate granulocytopenic patients at heightened risk for infection by measuring tissue-bound phagocytes, opsonizing antibody and local defense factors. We are seeking to improve rapid diagnosis of fungal infections by measuring circulating antigens and to define the role of viruses in infection in immunocompromised patients.

Effective management of the granulocytopenic patient requires empiric broad-spectrum antibiotic therapy. We are developing new therapeutic approaches based on new antibiotic developments, particularly the third generation cephalosporins. Our results show that a new cephalosporin, ceftazidime, is as effective as a triple drug combination. Our studies are also defining the appropriate antibiotic therapy for documented bacterial infections, the necessary duration of empiric therapy for patients with unexplained fever, the choice of empiric antifungal therapy, and the merits of empiric therapy vs invasive procedures in patients with pulmonary infiltrates.

To prevent infections we are continuing our study of total protected isolation for high risk patients but are developing new prevention strategies to improve host defenses. These include passive immunization with post-vaccine antisera to the core glycolipid of enterobacteriaceae as well as pooled immunoglobulins. Our preclinical studies are further focused on attaching (arming) leukocytes with polyclonal or monoclonal antibodies to improve their bactericidal activities and ultimately leukocyte transfusion therapy. We are also developing methods to accelerate granulopiesis using chemically-defined immuno-regulatory agents, and ultimately to study their mechanisms of action.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06840-09 PB

PERIOD COVERED
October 1, 1983, to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Treatment of Acute Leukemia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	David G. Poplack	Head, Leukemia Biology Section	PB, NCI
Others:	S. Zimm	Investigator	PB, NCI
	F. Balis	Investigator	PB, NCI
	R. Wesley	Senior Staff	BR, NCI

COOPERATING UNITS *(if any)*
Dept. of Pediatrics, Univ. of Pittsburgh (J. Blatt); Dept. of Medicine, Univ. of Montreal (J. Jolivet); Dept. of Pediatrics, Catholic Univ. of Rome (R. Riccardi); Laboratory of Neuropsychology, NIMH, NIH (P. Brouwers).

LAB/BRANCH
Pediatric Branch

SECTION
Leukemia Biology Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.0	3.0	2.0

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Clinical research into the biology and treatment of acute leukemia is pursued with particular emphasis on acute lymphoblastic leukemia (ALL) of childhood. Major issues being addressed include: 1) development of therapeutic strategies aimed at improving overall prognosis of children with ALL, 2) investigation into the mechanisms of treatment failure with particular emphasis on evaluation of pharmacologic approaches to leukemic therapy, and 3) characterization of adverse sequelae of antileukemic therapy and design of treatment regimens which avoid them.

The major ALL treatment protocol has successfully demonstrated that high-dose, protracted systemic methotrexate infusions can substitute for cranial radiation as central nervous system (CNS) preventive therapy for the majority of patients with ALL. Moreover, analysis of data derived from this study has identified a patient group at particular risk for CNS relapse. A new, high risk protocol has been devised in an attempt to improve the prognosis for these and other poor risk patients. Studies on the bioavailability of orally administered maintenance chemotherapy have demonstrated that many patients do not achieve adequate drug levels in the blood, raising concern over this possible mechanism of treatment failure. A major, multi-institutional pharmacologic monitoring protocol has been instituted in an attempt to study the relationship between the bioavailability of orally administered maintenance chemotherapy and relapse in children with ALL. The role of diurnal variation, concomitant food intake and inter-patient variability in intracellular drug metabolism are being explored as possible factors in treatment failure. Studies on late effects have demonstrated CT brain scan, neuroendocrine, and psychometric test abnormalities in long-term survivors of childhood ALL. These observations have stimulated the search for alternative, equally effective but less toxic methods of CNS preventive therapy.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06880-07 PB

PERIOD COVERED
October 1, 1983, to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Clinical Pharmacology; Experimental Approaches to the Treatment of CNS Malignancy.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	David G. Poplack	Head, Leukemia Biology Section	PB, NCI
Others:	S. Zimm	Investigator	PB, NCI
	F. Balis	Investigator	PB, NCI
	J. Collins	Senior Investigator	CPB, NCI
	J. Grygiel	Investigator	CPB, NCI
	P. Gormley	Senior Investigator	LCHPH, NCI

COOPERATING UNITS *(if any)*
Dept. of Pediatrics, Catholic Univ. of Rome (R. Riccardi); Dept. of Pediatrics, Children's Hospital of Los Angeles (J. Holcenberg); Pharmacy Department, CC, NIH (P. Narang).

LAB/BRANCH
Pediatric Branch

SECTION
Leukemia Biology Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
6.0	4.0	2.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The clinical pharmacology of antineoplastic agents used in the treatment of pediatric malignancies is studied. Emphasis is placed on the role of clinical pharmacologic monitoring and on both pre-clinical and clinical pharmacologic studies of Phase I agents. The clinical pharmacology of orally administered antileukemic agents has been evaluated and the limited bioavailability and variable drug levels of 6-MP achieved following oral administration has been documented. Studies are underway to determine the extent to which this phenomenon is the cause of treatment failure. The interaction of 6-MP and allopurinol, a unique example of hepatic first-pass metabolism in cancer chemotherapy has been examined in both subhuman primates and in man. Additional efforts to optimize 6-MP administration have been based on in vitro studies which have demonstrated a need for prolonged exposure to cytocidal concentrations of drug to maximize leukemic cell kill. A clinical protocol evaluating prolonged intravenous 6-MP infusions in a Phase I setting is underway. Pre-clinical and clinical pharmacokinetic studies of the new agent, Tiazofurin, have been pursued and a pediatric Phase I study of this agent is in progress.

A major effort of this project is to study experimental approaches to the treatment of both meningeal and non-meningeal CNS malignancy. A unique subhuman primate model which allows sterile, repetitive access to cerebrospinal fluid, is utilized to study the CNS pharmacokinetics of various intrathecally and intravenously administered chemotherapeutic agents; to evaluate the neurotoxicities attendant upon various CNS treatments; and to evaluate and screen in a pre-clinical setting newer CNS treatment modalities and drug schedules. Information gained from the studies with this model is then applied to the design of clinical treatment protocols. A clinical study of intrathecal AZQ is in progress. Pre-clinical studies evaluating intra-CSF drug administration via indwelling drug delivery devices is under way.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 06890-05 PB

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Lymphoma Biology and Epstein-Barr Virus

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Ian T. Magrath	Senior Investigator	PB, NCI
Others:	Jacqueline Whang-Peng	Senior Investigator	MB, NCI
	Stanley Korsmeyer	Senior Investigator	MET, NCI

COOPERATING UNITS *(if any)*

Flow Cytometry Lab., George Washington Univ. (O. Alabaster); NCI/Navy Medical Oncology Branch (L. Kirsch); Wistar Institute (C. Croce); Arthritis and Rheumatis Branch, NIADDKD (G. Tsokos); Lab. of Clinical Investigation, NIAID (T. Gaither)

LAB/BRANCH

Pediatric Branch, NCI

SECTION

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5	3	2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Undifferentiated B-cell lymphomas occur predominantly in children and young adults in a) a geographically delineated form, which is EBV associated, b) a sporadic, widespread form which is not EBV associated, and c) a form arising in certain immunodeficiency syndromes notably that occurring predominantly in homosexual drug abusers, which is also EBV associated. The goals of the present work are to gain information on the epidemiology, pathogenesis and biological differences among the several forms of undifferentiated lymphoma. Links have been established with a number of cancer centers in various parts of the world as part of a concerted effort to characterise, with more precision than has hitherto been achieved, differences in the spectrum of lymphoid neoplasia that occurs in different environments. Biological studies are carried out on cell lines derived from all three of the above categories of undifferentiated lymphomas. Of particular interest is the expression of genes involved in specific chromosomal translocations associated with these tumors, namely the immunoglobulin genes and c-myc oncogene, and changes in the expression of these genes during differentiation of the cell lines. We are interested to determine whether the expression of the translocated c-myc gene is a consequence of the stage of differentiation of the cell. We have derived a number of monoclonal antibodies raised against a Burkitt lymphoma cell line and are currently characterizing these. We hope to find monoclonal antibodies which will be of value in determining the normal counterpart cell of Burkitt's lymphoma. We are also studying the influence of chemotherapeutic agents on the expression of certain cell surface proteins. Methotrexate increases the expression of some proteins, for example HLA, and this phenomenon may be pertinent to therapy with monoclonal antibodies, hormones or other compounds which bind to cell receptors.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 00650-29 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Service Radiation Therapy

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	A. S. Lichter	Senior Investigator	ROB, NCI
Others:	T. Kinsella	Senior Investigator	ROB, NCI
	P. Findlay	Senior Investigator	ROB, NCI
	S. Hancock	Senior Investigator	ROB, NCI
	A. Zabell	Senior Investigator	ROB, NCI
	B. Kelly	Chief, Rad. Therapy Tech.	ROB, NCI
	A. Zola	Rad. Therapy Tech.	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Radiation Oncology Branch

SECTION
Radiation Therapy Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5	2	3

CHECK APPROPRIATE BOX(ES)

- [X] (a) Human subjects
  - [ ] (a1) Minors
  - [ ] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The objective of this project is to provide expert radiotherapy, consultation, and radiation therapy treatment for Clinical Center patients admitted to services other than the Radiation Oncology Branch of the NCI. Support is given to the Medicine Branch, Surgery Branch, Pediatric Branch, NCI/Navy Medical Oncology Branch, Neurosurgical Service, Endocrine Service, and other Federal Hospitals in the area where technical expertise and technical equipment dictate a need for such consultation.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 00684-29 RO

PERIOD COVERED

October 1, 1982 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Nonclinical Irradiation Services

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. van de Geijn	Physicist	ROB, NCI
Others:	F. Harrington	Engineering Technician	ROB, NCI
	B. Fraass	Staff Fellow	ROB, NCI
	R. Miller	Physicist	ROB, NCI
	J. Doolittle	Electronic Technician	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Radiation Oncology Branch

SECTION

Radiation Physics and Computer Automation Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.4	0.1	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Radiation Physics and Computer Automation Section provides radiation physics services, equipment, and advice on experiments involving radiobiology. Cells, tissue cultures, mice, rats and dogs are irradiated for radiobiology experiments. Current involvement concentrates on I-125 dosimetry related to monoclonal antibody studies.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06310-05 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Surgery Versus Radiation Therapy in Treatment of Primary Breast Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: P. A. Findlay Senior Investigator ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Radiation Oncology Branch

SECTION
Radiation Therapy Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
6	3	3

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this study is to determine whether a breast-conserving treatment program of limited surgery and definitive radiation offers equivalent local control and survival to mastectomy in patients with early stage breast cancer. After work-up confirms localized disease, patients are randomly assigned to either primary surgery or primary irradiation. Patients treated with mastectomy are offered breast reconstruction. All patients undergo complete axillary node removal; those patients with pathologically positive lymph nodes receive chemotherapy.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06313-05 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Dose to Lung and Opposite Breast vs. Technique for Primary Breast Irradiation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	B. A. Fraass	Physicist	ROB, NCI
Others:	A. S. Lichter	Radiotherapist	ROB, NCI
	J. van de Geijn	Radiation Physicist	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Radiation Oncology Branch

SECTION
Radiation Physics and Computer Automation Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.1	.1	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Treatment planning techniques for primary breast irradiation are investigated to optimize dose to areas at risk while minimizing dose to critical structures. When the high-dose volume is increased to include the internal mammary chain (IMC), dose to lung and opposite breast increases. This effect has been investigated extensively with both treatment planning and dose measurements.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 06319-05 RO

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Use of Prematurely Condensed Chromosomes (PCC) in Biological Dosimetry

PRINCIPAL INVESTIGATOR *(List other professionel personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: J. Mitchell Radiobiologist ROB, NCI

COOPERATING UNITS *(if any)*

Department of Radiation Biology, Colorado State University, Fort Collins, CO (J. Bedford).

LAB/BRANCH

Radiation Oncology Branch

SECTION

Radiation Biology Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1	.5	.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to determine if the use of premature chromosome condensation (PCC) technique will improve the resolution of the lymphocyte biological dosimetry system for low total doses of radiation (<10 rad). With the PCC technique, chromosomal damage (gross breaks in chromosomes) of interphase cells can be studied immediately following radiation exposure. Assays will be made before the cells have had time to repair many of the initial breaks, thereby increasing the number of breaks counted as opposed to counting aberrations conventionally 24-48 hours after exposure in metaphase I and II.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06320-05 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Response of Mammalian Cells to Chemotherapy Drugs

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	A. Russo	Clinical Associate	ROB, NCI
Others:	J. Mitchell	Radiobiologist	ROB, NCI
	B. DeGraff	Biologist	ROB, NCI
	J. Gamson	Biologist	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Radiation Oncology Branch

SECTION
Radiation Biology Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Several chemotherapy agents with proven utility, e.g., anthracyclines, bleomycins, and noble metal derivatives, are being studied. The detoxification mechanisms, modification of cellular response by biochemical manipulation of intracellular redox status, and oxygen metabolism, in sensitive and resistant cells are of interest. Deleterious species produced by the antineoplastic drugs, and cellular response to these species, as well as thiol compounds, and their metabolic interactions with the drugs, and labile species produced by the drugs are being examined. It has been demonstrated that depletion of cellular glutathione (GSH) by inhibitors of GSH synthesis sensitize cells to adriamycin and bleomycin while GSH elevation provides protection. These studies will provide a better understanding of the mechanisms of drug action.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06321-05 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Radiosensitization of Aerated and Hypoxic Mammalian Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. Mitchell	Radiobiologist	ROB, NCI
Others:	A. Russo	Clinical Associate	ROB, NCI
	T. Phillips	Visiting Scientist	ROB, NCI
	B. DeGraff	Biologist	ROB, NCI
	J. Gamson	Biologist	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Radiation Oncology Branch

SECTION
Radiation Biology Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4	2	2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

There is considerable evidence that the existence of hypoxic cells in human tumors may pose a problem for clinical radiotherapy. The purpose of this project is to study the effects of ionizing radiation delivered at different exposure rates with respect to cell killing, cell cycle status, and cellular redox potential of mammalian cells grown either under aerated or hypoxic conditions. A major portion of this study will be concerned with various means of modulating the cellular redox potential by using drugs that either deplete or elevate cellular glutathione (GSH). The indirect effects of GSH removal will be assessed by high performance liquid chromatography and gel electrophoresis. In addition, nitroimidazole radiosensitizers such as SR-2508 will be studied as hypoxic sensitizers as a function of intracellular sulphydryl concentrations. These studies should provide a better understanding of the effects of radiation to aerated and hypoxic cells.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06328-04 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Field Configuration in Definitive Radiotherapy of the Intact Breast

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	B. A. Fraass	Physicist	ROB, NCI
Others:	A. S. Lichter	Radiotherapist	ROB, NCI
	J. van de Geijn	Radiation Physicist	ROB, NCI
	F. Harrington	Engineering Technician	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Radiation Oncology Branch

SECTION
Radiation Physics and Computer Automation Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.2	.15	.05

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This work has resulted in the development and implementation of a new irradiation technique to produce in a more reliable fashion a uniform dose distribution in the breast tissue and the supraclavicular area. The necessary numerical data for routine application are obtained by using a specially developed computer program.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06329-04 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Clinical Radiation Physics Service

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. van de Geijn	Radiation Physicist	ROB, NCI
Others:	B. A. Fraass	Radiation Physicist	ROB, NCI
	R. W. Miller	Radiation Physicist	ROB, NCI
	F. Harrington	Engin. Tech.	ROB, NCI
	R. Creecy	Computer Specialist	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Radiation Oncology Branch

SECTION
Radiation Physics and Computer Automation Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
7.5	2.5	5.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Section provides expert physical and technological support for radiation treatment. This support consists of routine calibration and quality assurance of all radiation equipment and includes special dosimetry studies, computer-assisted treatment planning, and the design and development of special equipment tailored to special clinical needs. Regular checking of dosimetric and technical set-up aspects of radiation treatment to be continued.

1. An efficiently graded quality assurance program, originally developed for the two Siemens linear accelerators, has been adapted and extended for the three Varian accelerators (Clinacs 4, 18, and 20). A new quality assurance detector using five ionization chambers is being integrated into the QA program. This device will consolidate output, energy and symmetry checks and will be useful for electrons as well as photons.

2. Adaptation of the new radiation equipment has been performed and special supporting equipment for patient treatment has been developed and implemented.

3. The Clinac 4/100, Clinac 18 and Clinac 20 linear accelerators are now fully operational. Preparatory work for total skin and total body irradiation has been completed. Sufficient dosimetric work has been done to allow total body irradiation (TBI) and intraoperative radiotherapy to be performed on both

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06330-04 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Extension of a 3-D Dose Field Model

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. van de Geijn	Radiation Physicist	ROB, NCI
Others:	B. Fraass	Radiation Physicist	ROB, NCI
	R. Miller	Radiation Physicist	ROB, NCI
	R. Creecy	Computer Specialist	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Radiation Oncology Branch

SECTION
Radiation Physics and Computer Automation Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The capability to calculate the distribution of absorbed dose produced by photon beams and electron beams of the most general characteristics is of vital importance in radiotherapy. Conceptually, this new radiation field model takes as a basis the empirical distributions along three mutually perpendicular reference lines in a "master field" and mathematical expressions to describe the effect of variations of field size, depth and focal distance. This concept is applied to the beam-modifying devices as well. The approach is attractive from a theoretical as well as a practical point of view. The investigations include the generalization for irregular fields modified by irregular blocks for photon beams and electron beams, and the influence of inhomogeneities. The investigations of the problems posed by irregularly shaped and blocked external beams have been completed for photon beams. The extension to electron beams is continuing. Of special interest are the implications of the large number of electron energies and the need for flexible application of different energies and field shapes in combination with photon fields. The central ray distributions can now be described on the basis of only seven characteristic depth dose data points, for 60Co to 18 MV x-rays, using the concept of Net Fractional Depth Dose (NFD). The NFD formalism is currently being extended to the description of the influence of inhomogeneities, such as lung tissues.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06331-04 RO

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Computer-Assisted 3-D Radiation Treatment Planning

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. van de Geijn	Radiation Physicist	ROB, NCI
Others:	B. Fraass	Radiation Physicist	ROB, NCI
	R. Miller	Radiation Physicist	ROB, NCI
	R. Creecy	Computer Specialist	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Radiation Oncology Branch

SECTION

Radiation Physics and Computer Automation Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	3.0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this continuing project is the development and clinical implementation of a generalized system for external beam treatment planning. It will enable the optimum utilization of existing treatment facilities. The system is based on a generalized 3-D dose field model which covers photon and electron as well as neutron beams. The computer program and most of its clinical implementation was completed for the photon and electron fields available from the local Clinac 4, Clinac 8 and Clinac 20 linear accelerators. Much work is to be done on the implementation of the Microtron with its 2 photon energies and 9 electron energies and some unusual technical options. The current capabilities include interactive simulation of most irradiation techniques, including the effect of most beam modifying devices. Transverse patient contours are overlaid on corresponding CT scans so that dose distribution can be related to the anatomy. Three of the four new radiation machines have been implemented for routine treatment planning. Work is continuing on the transition of most of our computer programs to the VAX-11/750 system, from the old PDP 11/70 system. This work is complicated by the need for continuing reliable routine support for the clinical treatment.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06332-04 RO

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Clinical Use of a Match-Line Wedge for Radiation Field Matching

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	B. A. Fraass	Physicist	ROB, NCI
Others:	J. van de Geijn	Physicist	ROB, NCI
	E. Glatstein	Chief	ROB, NCI
	F. Harrington	Engineering Technician	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Radiation Oncology Branch

SECTION

Radiation Physics and Computer Automation Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.2	.15	.05

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is the development and clinical use of a useful method for matching adjoining megavoltage radiation fields so that the dose distribution through the match region is uniform. A "match-line wedge" has been developed which satisfies the above requirement. Simplicity of use has assured that the wedge is used routinely and effectively.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 06333-04 RO

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Dosimetry of Total Skin Electron Irradiation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	B. A. Fraass	Physicist	ROB, NCI
Others:	R. Miller	Health Physicist	ROB, NCI
	J. Doolittle	Electronic Technician	ROB, NCI
	E. Glatstein	Chief	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Radiation Oncology Branch

SECTION

Radiation Physics and Computer Automation Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.3	.2	.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A detailed study has been made of the dosimetry of total skin electron irradiation. This study has quantified and improved the whole skin treatments received by patients with mycosis fungoides. The treatment technique is being updated and implemented on the new Clinac 20 linear accelerator.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 06334-04 RO

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Dose to Gonads from Radiation Treatment for Lymphomas and Sarcomas

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	B. A. Fraass	Physicist	ROB, NCI
Others:	T. J. Kinsella	Radiotherapist	ROB, NCI
	K. Yeakel	Dosimetrist	ROB, NCI
	J. Caulkins	Health Technician	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Radiation Oncology Branch

SECTION

Radiation Physics and Computer Automation Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.25	.2	.15

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Doses to gonads have been measured on patients who are irradiated as part of their treatment for lymphomas or sarcomas. Ion chambers and thermoluminescent dosimetry (TLD) measuremnts have been made to verify the measurements on patients. Two very effective gonadal shields have been built and put into routine clinical use.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 06337-04 RO

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Real-Time Radiotherapy Treatment Monitor

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	B. A. Fraass	Physicist	ROB, NCI
Others:	J. Doolittle	Electronics Technician	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Radiation Oncology Branch

SECTION

Radiation Physics and Computer Automation Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.05	.02	.03

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of the project is to develop a real-time monitor for radiation treatments. Although routine quality assurance is the immediate aim, continued development will make feasible many projects which rely on real-time patient dose monitoring.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06343-04 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Phase 1 Study of Intravenous Bromodeoxyuridine (BUdR) (NSC38297)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T. J. Kinsella	Senior Investigator	ROB, NCI
Others:	A. Russo	Clinical Associate	ROB, NCI
	J. B. Mitchell	Radiobiologist	ROB, NCI
	E. Glatstein	Chief	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Radiation Oncology Branch

SECTION
Radiation Therapy Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	2.0	

CHECK APPROPRIATE BOX(ES)

- [x] (a) Human subjects
  - [ ] (a1) Minors
  - [ ] (a2) Interviews
- [x] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Bromodeoxyuridine (BUdR), a known radiosensitizing drug is given as a continuous intravenous infusion in patients with high-grade primary brain tumors and other poorly radioresponsive tumors. The drug is infused for 24 hours daily for up to 14 days with most patients receiving two separate 2 week infusions of BUdR. Over the last 6 months, we have treated six patients with progressive metastatic liver disease usually from a colorectal primary combining the infusion with liver radiation. The radiation therapy is given as a fractionated scheme with daily doses of 200-250 rad delivered through APPA fields to total dose of 2500-3000 rad. We have also continued to follow an additional group of 33 patients who were treated prior to October 1, 1983, with either intermittent (12 hours per day) or continuous (24 hours) infusions of BUdR on the schedule as outlined above.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06345-04 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Study of Radiosensitizer, Misonidazole (NSC 261037)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
PI: S. Hancock Senior Investigator ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Radiation Oncology Branch

SECTION
Radiation Therapy Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Pharmacokinetic and toxicity studies were performed on patients undergoing treatment with misonidazole, a nitroimidazole radiosensitizing agent. The intent of establishing pharmacokinetics of this agent was met prior to the current period and no further patients have been accrued on this study.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06348-03 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Interactive Linear-Source Brachytherapy Dosimetry Program

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
PI: R. W. Miller Radiation Physicist ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Radiation Oncology Branch

SECTION
Radiation Physics and Computer Automation Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.1	.1	0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to develop an interactive computer program for calculating dose distributions in an arbitrary plane from arrays of filtered, linear radioactive sources used primarily for intercavitary radiotherapy. The sources used are 137 Cs capsules with stainless steel walls. Dose distributions are calculated using the Sievert Integral with experimentally determined attenuation coefficients.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 06349-03 RO

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Relationship of Cellular Redox State and Thermotolerance

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	A. Russo	Clinical Associate	ROB, NCI
Others:	J. Mitchell	Radiobiologist	ROB, NCI
	B. DeGraff	Biologist	ROB, NCI
	J. Gamson	Biologist	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Radiation Oncology Branch

SECTION

Radiation Biology Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4	2.5	1.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Hyperthermia is currently being evaluated as a potential cancer treatment modality. The mechanism(s) of hyperthermia killing and the induction of thermal resistance (thermotolerance) are not known. We will examine the role of the cellular reduction potential during and after heating to determine its role or alteration during thermal stress. This will be accomplished by using drugs which either bind glutathione (GSH) or prevent its synthesis. There appears to be a relationship between the synthesis of heat shock proteins and the induction of heat resistance. The effect of thiol modulation will be studied in the context of heat shock proteins. Recently, several compounds have been introduced which elevate cellular GSH. These compounds will be synthesized and evaluated in regard to thermal response.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06350-02 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
A Phase I Trial of the Hypoxic Radiosensitizer, SR-2508

PRINCIPAL INVESTIGATOR *(List other professionel personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: S. L. Hancock Senior Investigator ROB, NCI

COOPERATING UNITS *(if any)*
Radiation Therapy Oncology Group: Stanford University (C. N. Coleman), University of Alberta (R. C. Urtasun), Washington University (T. H. Wasserman), and University of California (J. W. Harris).

LAB/BRANCH
Radiation Oncology Branch

SECTION
Radiation Therapy Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This is a Phase I trial of the radiation sensitizer, SR-2508, which is conducted in conjunction with the Radiation Therapy Oncology Group. SR-2508 is a nitroimidazole derivative which was designed to be less lipophilic than its predecessor compounds, misonidazole and desmethylmisonidazole. Preclinical studies indicated that SR-2508 was markedly less toxic to peripheral nerves than prior hypoxic cell radiosensitizers used in clinical trials. The trial has found that up to 3.4 grams per meter squared of SR-2508 can be administered 3 times weekly for 3 weeks in conjunction with standard radiotherapy with less than 50% risk of a limited, grade I peripheral neuropathy. This study has since employed lower daily doses of SR-2508 and it currently appears that 1.7 grams per meter squared may be administered four times per week throughout a six week course of irradiation. Pharmacokinetic data has been generated on the patients entered in this trial, and it appears that the area under the curve calculations of drug exposure are relatively good predictors for the development of peripheral neuropathy.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06351-02 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Response of Human Hematopoietic Precursor Cells to Halogenated Pyrimidines

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. B. Mitchell	Radiobiologist	ROB, NCI
Others:	A. Russo	Clinical Associate	ROB, NCI
	T. Kinsella	Senior Investigator	ROB, NCI
	G. Morstyn	Clinical Associate	ROB, NCI
	B. DeGraff	Biologist	ROB, NCI
	J. Gamson	Biologist	ROB, NCI
	T. Phillips	Visiting Scientist	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Radiation Oncology Branch

SECTION
Radiation Biology Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

When certain halogenated pyrimidines such as bromodeoxyuridine (BUdR) and iododeoxyuridine (IUdR) are incorporated into cellular DNA, the cells become more sensitive to ionizing radiation. This observation has lead to several clinical studies over the years and recently at the NCI to evaluate whether selective sensitization of tumors could be achieved by BUdR/IUdR infusion followed by radiation. An important question arises in these studies regarding whether or not the drug actually is incorporated into cells. This study proposes to obtain information regarding this question by using: a) cell survival determinations of pre and post infusion bone marrow precursor cells; b) whether or not sister chromatid staining can be observed in bone marrow stem cells; and c) use of a BUdR/IUdR monoclonal antibody and HPLC assays to actually quantitate the amount of BUdR/IUdR in tumor compared to normal tissue.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 06352-02 RO

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Relaxation Agents for NMR Diagnostic Imaging

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: O. A. Gansow Senior Investigator ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Radiation Oncology Branch

SECTION

Inorganic and Radioimmune Chemistry Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Nuclear Magnetic Resonance imaging is fast becoming a most powerful method for the non-invasive diagnosis of disease. A fundamental limitation of the technique derives from the fact that images are constructed from Tl relaxation time measurements of protons in the various biological "compartments". If Tl values for differing soft tissue types are similar, the type will not, in general, be resolvable in the images. A potential method for improving this situation is the development of relaxation agents which specifically alter Tl relaxation rates in tissues where they may be concentrated. We propose to design and construct such in vivo relaxation agents.

A study of concentration dependence of Tl relaxation by various metal chelates and organic nitroxyl radicals has been prepared. Based on these studies, the metal chelates appear to be more efficient.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06353-02 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Metal Chelate Conjugated Monoclonal Antibodies for Tumor Diagnosis and Therapy

PRINCIPAL INVESTIGATOR *(List other professionel personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	O. A. Gansow	Senior Investigator	ROB, NCI
Others:	R. W. Atcher	Expert	ROB, NCI
	M. Brechbeil	Chemist	ROB, NCI

COOPERATING UNITS *(if any)*
Johns Hopkins Medical School, Baltimore, MD (M. Strand); Argonne National Laboratory, Argonne, IL (A. Friedman).

LAB/BRANCH
Radiation Oncology Branch

SECTION
Inorganic and Radioimmune Chemistry Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.3	1.3	1.0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Tumor-associated monoclonal antibodies are potential therapeutic agents as selective carriers of cytotoxic agents to malignant cells. We are testing this hypothesis in two animal model systems: a tumor virus induced leukemia of mice and human tumor xenographs in nude athymic mice.

The various cytocidal agents being employed are radioisotopes. Their relative therapeutic efficacy when conjugated to antibodies is being assayed and compared to that of monoclonal antibodies alone. The isotopes to be employed include the highly tumoricidal alpha emitting parent radioisotopes Pb-212 or Bi-212. The syntheses of different chelates and radiochemical separations required for these objectives are being devised and reduced to clinical practice. Results from isotopic therapy are being compared with those obtained by use of antibody conjugated toxins or drugs with respect to tumor growth, regression or cure.

These studies will provide for human medicine a basis for design or rational therapy of malignancies by selectively targeting cytocidal agents to tumors as well as metastases.

New chelates for use in this project have been synthesized and are in testing.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06354-02 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Iron-57 Nuclear Magnetic Resonance: A New Tool for Biomedical Research

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
PI: O. A. Gansow Senior Investigator ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Radiation Oncology Branch

SECTION
Inorganic and Radioimmune Chemistry Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues x☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We are developing Iron-57 Nuclear Magnetic Resonance (NMR) as an experimental method for use in the Biomedical Sciences.

Numerous molecules essential to life are constructed about iron-containing central cores. Among these are hemoglobin, ferridoxin and the cytochromes. To date, no physical chemical methods have allowed direct study of the central metal environment of these proteins. Iron-57 nmr, i.e. the direct detection of the iron nmr signal, is being developed for that purpose.

We have recently reported results of an Iron-57 NMR investigation of characteristic relaxation times and chemical shifts of some iron compounds. The data furnished information on the chemical shift range of iron coordinated to nitrogen, substituent effects on Iron-57 chemical shifts, and relaxation mechanisms for Iron-57, and thus provide the basic parameters needed for further development of Iron-57 NMR.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06355-02 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Total Skin Electron Beam Radiation for AIDS Associated Kaposi's Sarcoma

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: P. A. Findlay Senior Investigator ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Radiation Oncology Branch

SECTION
Radiation Therapy Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.25	1.75	.50

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The NCI and NIAID of the NIH are currently investigating and treating patients with the newly described acquired immune deficiency syndrome (AIDS). About 30% of the patients with AIDS have Kaposi's Sarcoma (KS) a skin malignancy that has the capacity to spread to lymph nodes and internal organs. A significant proportion have KS limited to the skin and oropharyngeal mucous membranes. In patients without AIDS, KS has been very responsive to radiation therapy. In order to avoid the immunosuppressive effects of chemotherapy in those patients with limited disease, and in an attempt to prevent visceral spread by gaining control over skin disease, we are engaged in a trial of electron beam radiation to the entire skin. With this technique, the penetration of ionizing radiation will be limited to a depth of the patient, of less than 1 cm., which should not have an adverse effect on these patients already compromised immune systems.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06356-01 RO

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Treatment of Malignant Brain Tumors with Interstitial Radiotherapy

PRINCIPAL INVESTIGATOR *(List other professionel personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P. A. Findlay	Senior Investigator	ROB, NCI
Others:	R. Miller	Health Physicist	ROB, NCI
	P. Kelley	Nurse Specialist	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Radiation Oncology Branch

SECTION

Radiation Therapy Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4	3	1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Results of current therapy of most malignant adult brain tumors remain disappointing. Despite the most aggressive multimodality treatment, median survival in the most common tumor, glioblastoma multiforme, is 10 months and cure is anecdotal. These tumors extend beyond the limits of surgical resection and total dose of conventional external beam radiotherapy is limited by surrounding normal brain tolerance. By placing radioactive seeds of I 125 directly into the tumor bed we hope to achieve: 1) a high radiation dose to the tumor; 2) a low radiation dose to surrounding normal brain; and 3) increased therapeutic ratio with radiation delivered at low dose rates.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06357-01 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Clinical Studies on Intraoperative Radiation Therapy

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T. J. Kinsella	Senior Investigator	ROB, NCI
Others:	Z. Tochner	Visiting Associate	ROB, NCI
	E. Glatstein	Chief	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Radiation Oncology Branch

SECTION
Radiation Therapy Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
10	10	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Radiation Oncology and Surgery Branches of the National Cancer Institute have been involved in prospective randomized trials evaluating the potential role of intraoperative radiotherapy in three major disease sites including resectable carcinomas of the pancreas, resectable carcinomas of the stomach and resectable retroperitoneal sarcomas. We have also been involved in a single arm pilot trial involved in dose escalation of intraoperative therapy in selected patients whose locally advanced tumor are felt unlikely to be cured by standard therapy and at least there is a theoretical advantage for the use of intraoperative radiation therapy. Finally, as of September, 1983, we are involved in a randomized prospective trial evaluating a combination of intraoperative radiation and external beam radiation compared to conventional external beam radiation alone in patients with unresectable pancreatic carcinomas. To date, 80 patients have been treated with experimental intraoperative radiation therapy on these various protocols and there are an additional 45 other patients being followed as control patients on the various randomized prospective trials. We have clearly demonstrated that it is technically possible to combine intraoperative radiation therapy with a radical surgical procedure and that the acute morbidity from the combination is quite acceptable. To date, there does not appear to be any significant difference in the randomized prospective trials with respect to a local control, disease free survival, and overall survival. Obviously, these trials are ongoing and require more patients and further follow-up. Patients also need to be followed for any potential late effects of intraoperative radiation therapy.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06358-01 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Effects of γ -Irradiation on Cells and Their Constituents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P. Riesz	Research Chemist	ROB, NCI
Others:	M. Faraggi	Visiting Scientist	ROB, NCI
	R. Samuni	Visiting Scientist	ROB, NCI
	A. Carmichael	Visiting Fellow	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Radiation Oncology Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	3.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The effects of ionizing, ultraviolet radiation and ultrasound on cells and their constituents are being studied. The modification of radiation damage in DNA by cancer chemotherapy agents of the intercalating and alkylating types is of interest since such information is useful for combined modality treatment in radiation therapy. In relation to photodynamic therapy with hematoporphyrin derivative, we have studied the photosensitizing reactions of porphyrin derivatives. It was found that the spin trap 5,5 dimethyl-1-pyrroline-N-oxide is converted by certain photoexcited porphyrins to a characteristic Electron Spin Resonance (ESR) detectable species which is the product of singlet oxygen oxidation. Photolysis of certain metalloporphyrins at pH 11 lead to the formation of hydroxyl radicals detectable by spin trapping and ESR. The photodynamic action of adriamycin, daunomycin and mitoxantrone in the presence of peptides or nucleic acids was investigated. When adriamycin and daunomycin are photoirradiated in the presence of oxygen, superoxide anion radicals are generated, indicating that the photodegradation of DNA in the presence of these drugs is mediated by dissolved oxygen. New photosensitized reactions by several FDA certified food colors have been discovered. Continuing our studies of the effects of ultrasound on aqueous solutions, we have found that 1 microsecond pulses of 1 megahertz ultrasound bring about transient cavitation and the formation of OH and H radicals under diagnostic exposure conditions. Recently we have studied the feasibility of detecting free radicals in human red blood cells and V79 Chinese hamster cells by ESR and spin trapping. Generating radicals by γ -radiation or by adriamycin and using appropriate radical scavengers and line broadening agents it is possible to distinguish between endo and exo cellular formation of radicals.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06359-01 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
A Phase 1 Study of Iododeoxyuridine (NSC39661) Given as a Intravenous Infusion

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T. J. Kinsella	Senior Investigator	ROB, NCI
Others:	A. Russo	Clinical Associate	ROB, NCI
	J. B. Mitchell	Radiobiologist	ROB, NCI
	E. Glatstein	Chief	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Radiation Oncology Branch

SECTION
Radiation Therapy Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	2.0	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Iododeoxyuridine (IUdR) is a known radiosensitizing drug which is being delivered as a constant intravenous infusion for 12 hours every 24 hours for up to 14 days in patients with high grade primary brain tumors and other poorly radioresponsive tumors. The drug is being used as a clinical radiosensitizer and being combined with high-dose radiation therapy in an attempt to improve the response rate of these poorly radioresponsive tumors as well as to assess the toxicity both local and systemic of this radiosensitizer. To date, 16 patients have been entered on to this trial including 7 patients with glioblastoma and 9 other patients with other poorly radioresponsive tumors including soft tissue sarcomas and osteosarcomas which have been deemed unresectable. Patients are treated with twice daily fractions of radiation therapy given in two separate sessions and combined with two separate infusions of IUdR.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06360-01 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Radionuclide Generators to Produce Alpha-Emitters

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: R. Atcher Expert ROB, NCI

COOPERATING UNITS *(if any)*
Chemistry Division, Argonne National Laboratory, Argonne, IL (A. Friedman).

LAB/BRANCH
Radiation Oncology Branch

SECTION
Inorganic and Radioimmune Chemistry Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This work involves the design, testing and use of radionuclide generators to produce alpha emitters to be attached to proteins for use in radiotherapy. The generation of systems in use now requires the use of Th-228 as the radionuclide parent. The long half life, two years, makes it unsuitable for use by personnel without training in the handling of long-lived activity.

We have undertaken a project with the Chemistry Division at Argonne National Laboratory to develop a new generator system based on the parent, Ra-224. This radionuclide has a 3.5 day half life, reducing the potential problems associated with a long lived radionuclide. We designed and tested a separation system to remotely separate thorium and radium in a manipulator-equipped shielded cave. We have recently completed renovations to a facility which will be devoted to this work.

Simultaneously, we have developed a new generator which will use the radium parent. This system uses a disposable generator package to minimize shipping and handling. This system utilizes an organic cation exchanger which is eluted with hydrochloric acid to yield either the bismuth daughter or lead daughter. Test with a small scale generator have shown yields in the range of 80 percent with negligible breakthrough of the radium parent.

Similar results have been seen with the thorium-radium separation. This system will house 750 millicuries of Th-228. Once in operation, we will receive generators on a regular (monthly or semi-monthly) basis. They will yield approximately 20 millicuries of activity, an order of magnitude higher than what is currently available.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 06361-01 RO

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 charecters or less. Title must fit on one line between the borders.)*

Phototherapy of Murine Ovarian Cancer by Hematoporphyrin Derivative

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	A. Russo	Clinical Associate	ROB, NCI
Others:	Z. Tochner	Visiting Scientist	ROB, NCI
	M. Aiken	Biologist	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Radiation Oncology Branch

SECTION

Radiobiology Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2	1.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The use of hematoporphyrin derivative (HPD) in combination with red light is currently under investigation as an anti-cancer treatment modality. A major advantage of this therapy is the purported selectivity of tumor versus normal tissue response. Studies have been designed and are currently underway to establish HPD retention in normal versus tumor tissue in a murine model. An ovarian tumor model will be used to determine the pharmacodynamics of HPD, optimization of HPD delivery, laser penetration, dose, and timing of drug and light delivery within the peritoneal cavity.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 06362-01 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Single Copy Inverted Repeats Associated with Regional Genetic Duplications

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
PI: A. J. Fornace Cancer Expert ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Radiation Oncology Branch

SECTION
Radiobiology Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This was a continuation of a project initiated in Jerry Crabtree's laboratory (Laboratory of Pathology, DCBD, NCI). There I found that a portion of an exon in the human gamma fibronogen gene was duplicated approximately 1 kbp away in an adjacent intron. The duplication was flanked by a long inverted repeat sequence (IR) which was found to be single copy by Southern blot analysis. The structure of this duplication was reminiscent of transposable elements in lower eukaryotes and prokaryotes and had some sequence homology with the FB transposable elements in Drosophilia. Since 1-2% of most eukaryotic genomes consist of single copy IR, this may represent a major type of genetic duplication. Recently, a second single copy IR was identified in the murine immunoglobulin locus. By sequence analysis, I found that it also flanked a region which was duplicated 1 kbp away. Thus, it appears likely that many or most single copy IR in mammalian genomes are probably associated with regional genetic duplications. Therefore, it is possible that this type of genetic duplication constitutes a major type of regional duplicaton in eukaryotic evolution.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06363-01 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 charecters or less. Title must fit on one line between the borders.)*
Transcription in Alkylation Hypersensitive Human Tumor Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
PI: A. Fornace Cancer Expert ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Radiation Oncology Branch

SECTION
Radiobiology Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.2 (ROB only)	0.2	0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Day and others have shown that approximately 20% of human tumor lines and viral transformed human lines are hypersensitive to alkylating agents due to an apparent absence of O to the sixth power-methylguanine methyltransferase. Since this "enzyme" acts as a suicide protein and is inactivated in the reaction with the damaged base, it is relatively abundant in normal cells - up to 10 to the sixth power per cell. If the defect in mer- cells is at the level of transcription, then mRNA species absent in mer+ cells could be enriched by hybridization subtraction procedures using cDNA probes from mer+ cells. In collaboration with R. Day and D. Yarosh, this has been done. Such probes have been used to screen a normal human cDNA library and a variety of cDNA clones have been isolated. We plan to further characterize such isolates by measuring their abundance in RNA from a variety of mer+ and mer- cell lines.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 06364-01 RO

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Measurement of DNA Damage in Human Cells by Alkaline Elution and Endonucleases

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	A. J. Fornace	Cancer Expert	ROB, NCI
Others:	T. J. Kinsella	Senior Investigator	ROB, NCI
	J. B. Mitchell	Radiobiologist	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Radiation Oncology Branch

SECTION

Radiobiology Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	0.7	0.8

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Measurement of DNA damage with endonucleases, which recognize lesions such as pyrimidine dimers or ionizing radiation base damage, has been used to study DNA repair in mammalian cells (Patterson, Adv. Radiat. Biol. 7: 1, 1978). The sensitivity of this approach has been increased 1 to 2 orders of magnitude by adapting it to the alkaline elution technique (Fornace, Mutation Res. 94: 263, 1982). In the case of ionizing radiation, enzyme preparations from M. luteus or E. Coli can now be used to detect base damage and its repair in human cells after biologically relevant doses. We have recently concluded dose response and repair kinetic studies in normal human fibroblasts after X-irradiation. We have initiated studies using X-ray sensitive strains, such as from patients with ataxia telangiectasia.

In the case of UV-radiation, our approach has been used to show that a small fraction of pyrimidine dimers are exchanged into DNA synthesized after UV by a recombination process somewhat analogous to recombination repair in bacteria (Fornace, Nature 304: 552, 1983). Possible abnormalities in recombination repair will be studied in likely cancer-prone diseases such as Bloom's syndrome and the variant form of xeroderma pigmentosum.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06365-01 RO

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: RNA Transcripts Induced by Hyperthermia in Rodent Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	A. Fornace	Cancer Expert	ROB, NCI
Others:	J. B. Mitchell	Radiobiologist	ROB, NCI
	A. Russo	Clinical Associate	ROB, NCI

COOPERATING UNITS *(if any)*:

LAB/BRANCH: Radiation Oncology Branch

SECTION: Radiobiology Section

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.3	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Prokaryotic and eukaryotic cells respond to environmental stress by the induction of a variety of stress-related proteins. In mammalian cells, the most well characterized group of stress proteins are induced by hyperthermia. Transcription of heat shock proteins increases markedly after hyperthermia and several of these genes have been cloned from HeLa cells in other laboratories. It is likely that transcription of other genes is also induced in mammalian cells since approximately 10-20 genes are induced in prokaryotes and lower eukaryotes. One approach to isolate such transcripts is to enrich for heat shock specific cDNA's by hybridization subtraction with mRNA from control cells. We have done this with rodent cells, V79. We are currently constructing a cDNA library with this enriched cDNA. The eventual aim is to characterize the response of V79 cells to hyperthermia.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 06366-01 RO

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Nuclear Magnetic Resonance Studies on Mammalian Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. B. Mitchell	Radiobiologist	ROB, NCI
Others:	A. Russo	Clinical Associate	ROB, NCI
	B. DeGraff	Biologist	ROB, NCI
	A. Zabell	Radiotherapist	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Radiation Oncology Branch

SECTION

Radiobiology Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Cell systems have been developed to dynamically monitor ATP levels in cells by nuclear magnetic resonance (NMR). We have demonstrated that hyperthermia treatment and alteration of glutathione levels do not affect ATP metabolism. Further, the lack of ATP signals in cells was shown not to be an indicator of cell death as assayed by cloning forming ability. Studies are designed to study the effects of pertubations of the respiratory chain and redox cycle on ATP metabolism. Work is underway to synthesize non-toxic, specific NMR contrast reagents for resolving hypoxic centers within the tumor. This will allow for better treatment planning in the clinic.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06367-01 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Mechanisms of Radioprotection

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	A. Russo	Clinical Associate	ROB, NCI
Others:	J. B. Mitchell	Radiobiologist	ROB, NCI
	B. DeGraff	Biologist	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Radiation Oncology Branch

SECTION
Radiobiology Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Thiols have long been studied as radioprotective compounds, yet the mechanism of protection is still poorly understood. We have developed means by which the major cellular thiol, glutathione, can be either depleted or elevated and then access radiosensitivity. We have shown that glutathione is not a major protector for X-ray. Plans are to synthesize compounds varying in chemical structure that may provide radioprotection.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 06368-01 RO

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Determination of pH in Human Tumors

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T. J. Kinsella	Senior Investigator	ROB, NCI
Others:	Z. Tochner	Visiting Scientist	ROB, NCI
	J. B. Mitchell	Radiobiologist	ROB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Radiation Oncology Branch

SECTION

Radiobiology Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2	1.0	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Both hyperthermia treatment and certain chemotherapy drugs have been shown to be more effective if treatment is conducted at low pH (6.7 - 7.0). Should tumors possess regions of low pH due to nutrient depletion and compromised circulation, these findings would have clinical implications. While several laboratories and clinics have measured the pH in small tumors, data regarding large tumors is lacking. Using a specially designed fiber optic pH probe, tumor pH at various sites will be determined for large pancreatic tumors. Pathology at the site of pH measurement will also be determined. These data will be compared to the pH of normal tissue.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06369-01 RO

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Radiation Characteristics of a 22 MeV Medical Microtron

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	R. W. Miller	Health Physicist	ROB, NCI
Others:	J. van de Geijn	Physicist	ROB, NCI

COOPERATING UNITS *(if any)*
Scanditronix, Essex, MA (T. Cook).

LAB/BRANCH
Radiation Oncology Branch

SECTION
Radiation Physics and Computer Automation Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	1.8	1.2

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Physics Section is involved in studying the radiation characteristics of photon and electron beams produced by the Scanditronix MM-22 Medical Microton as part of acceptance testing and dosimetry prior to clinical use. Investigations and concurrent technical adaptations and changes have lead to flatness of the radiation fields and depth doses that are generally superior to similar beams from medical linacs. In addition, several shortcomings relative to dosimetry and specific beam characteristics were discovered and are being corrected. These include:

1. Inclusion of a dose rate compensation circuit to correct dose-rate dependence of the monitor chamber at high dose rates.

2. Modification of the dose rate servo circuits and inclusion of separate settings for the AGPS for each energy to improve dose rate stability.

3. Complete reworking of the 22 MeV electron beam. By using a thinner primary scattering foil and special secondary foil, the penetration has been substantially improved. Additionally, X-ray contamination has been markedly reduced.

Also, the dosimetric aspects of asymmetric collimator jaws are being investigated. It has also been shown that their use with intraoperative applicators can virtually eliminate the "hot spot" due to the cone bevel.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 03800-14 SURG

PERIOD COVERED: October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Surgical Consultants & Collaborative Research Involving Surgical Services at NIH

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	S.A. Rosenberg	Chief of Surgery, NCI	SURG NCI
Others:	Entire Staff	Surgery Branch	SURG NCI

COOPERATING UNITS *(if any)*: GD Aurbach (NIAMDD), JL Doppman (CC), E Glatstein (NCI), J Robbins (NIAMDD), L Liotta (NCI), RC Young (NCI), P Pizzo (NCI), J Gardner (NIAMDD)

LAB/BRANCH: Surgery Branch

SECTION: Office of the Chief

INSTITUTE AND LOCATION: NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
7.0	5.0	2.0

CHECK APPROPRIATE BOX(ES)

- [x] (a) Human subjects
  - [ ] (a1) Minors
  - [ ] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Surgery Branch of the National Cancer Institute are the general surgeons and general surgical consultants to the entire National Institutes of Health. In this role we see patients for elective consultations as well as all emergency general surgical problems. Many collaborations on clinical studies have resulted from these consultative efforts.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 03801-14 SURG

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Clinical Studies in Cancer Surgery

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: S. A. Rosenberg Chief of Surgery, NCI SURG NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Surgery Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
10.6	7.6	3.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Surgery Branch has a variety of studies investigating innovative therapies for patients with malignant disease. The major emphasis of these studies is in the treatment of soft tissue sarcomas, osteogenic sarcomas, colorectal cancer, pancreatic cancer, and gastric cancer. The major-emphasis in Surgery Branch cancer therapy is in adjuvant therapy with emphasis on the use of multiple treatment modalities in addition to surgery.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 03811-10 SURG

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Immunotherapy of Animal and Human Sarcomas

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: S.A. Rosenberg Chief of Surgery SURG NCI

Others: L Grimm (Expert), S Shu (Expert), J Mule (Staff Fellow), D Weiland (Medical Staff Fellow), A Rayner (Medical Staff Fellow), S Schwarz (Biologist), P Spiess (Biologist), D Wilson (Microbiologist) SURG NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Surgery Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
7.5	4.0	3.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Attempts are being made to develop adoptive immunotherapeutic techniques utilizing the transfer of cells grown in long-term culture in interleukin-2. Techniques for the prolonged growth of cytotoxic and proliferative T cell lines and clones with anti-tumor reactivity have been developed. These cells have been shown to mediate the immunologic rejection of allografts and syngeneic tumors and attempts to use these cells in the adoptive immunotherapy of mouse and human tumors are in progress. A new class of cytotoxic cells has been described in both the mouse and the human. These lymphokine activated killer (LAK) cells develop selective cytotoxicity for cancer cells following incubation in the lymphokine, interleukin-2. The adoptive transfer of these cells into mice bearing established tumors can mediate the inhibition of pulmonary metastases. The systemic administration of interleukin-2 has been shown to enhance immune responses in vivo.

In the past year, two new immunotherapeutic trials have begun that utilize the adoptive transfer of lymphokine activated killer cells into patients with advanced cancer. In the past year, we have characterized a new recombinant interleukin-2 in the human and have begun clinical trials to study the in vivo effects of systemic administration of this material.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06652-08 SURG

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies of Immune Regulation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigetor.) (Name, title, laboratory, and institute affiliation)*

PI:	P.H. Sugarbaker	Head, Colorectal Cancer Section	SURG NCI
Others:	D. A. August	Medical Staff Fellow	SURG NCI
	H. L. Deutsch	Medical Staff Fellow	SURG NCI
	R. T. Ottow	Visiting Fellow	SURG NCI
	W. Matthews, Jr.	Chemist	SURG NCI
	F. J. Gianola	Physician's Assistant	SURG NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Surgery Branch

SECTION

Colorectal Cancer Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland, 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The work in this laboratory includes three major projects: 1) Assessment of alterations in the immune response brought about through the administration of passively administered alloantibody. The effects of alloantibody on retransplanted skin grafts is currently under investigation. 2) Studies on the use of activated cells to destroy tumor cells both in vivo and in vitro are underway. Biological response modifiers used to activate tumor cells include interleukin-2 and gamma interferon. An adjuvant immunotherapeutic attack on cancer cells remaining after surgery is planned using in vitro activated cells. 3) A new mechanism of specific suppression to facilitate the transplantation of tissue in skin allografts is being attempted. The use of antigen specific suicide with ^{3}H-thymidine to produce clonally depleted cell populations is being explored.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06654-07 SURG

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies in Malignant Disease

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	W.F. Sindelar	Senior Investigator	SURG NCI
Others:	G. Rong	Visiting Fellow	SURG NCI
	J. Glenn	Medical Staff Fellow	SURG NCI
	J. Chin	Medical Staff Fellow	SURG NCI
	S. Kurtzman	Medical Staff Fellow	SURG NCI
	L. Judson	Microbiologist	SURG NCI

COOPERATING UNITS *(if any)*

T. Kinsella, Senior Investigator, Radiation Oncology Branch, NCI
A. DeLuca, Biologist, Radiation Oncology Branch, NCI

LAB/BRANCH

Surgery Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.0	4.0	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Patients with gastrointestinal carcinomas are studied for evidence of reactivity against tumor-associated determinants expressed on both fresh and cultured syngeneic or allogeneic tumor cells using immunofluorescence and immunoperoxidase staining techniques. Various human malignant cell lines have been established in vitro and are being characterized morphologically and immunologically. An experimental model of pancreatic carcinoma has been developed in hamsters. Tumor-associated antigens have been isolated from both animal and human pancreatic cancers and are being investigated for possible applications to immunotherapy or methods of immunodiagnosis. Tissue-specific antigens have been isolated and are being investigated for possible use in immunotherapy of pancreatic carcinoma. Monoclonal antibodies have been developed to tumor-associated determinants in pancreatic cancers. Tolerance of normal and surgically-manipulated tissues to intraoperative radiotherapy is being investigated in dogs.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 06655-04 SURG

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Factors Influencing Host Cellular and Humoral Immune Responses to Neoplasia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Jack A. Roth, M.D. Senior Investigator, SURG, NCI
Harvey I. Pass, M.D., Senior Staff Fellow, Surgery Branch, NCI

Others: William K. Funkhouser, M.D., Medical Staff Fellow, SURG, NCI
Joe Billy Putnam, M.D., Medical Staff Fellow, SURG, NCI
Robert S. Ames, Biologist, SURG, NCI
Emile E. Trahan, Medical Technician, SURG, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Surgery Branch

SECTION

Thoracic Oncology Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Our laboratory has focused on factors that influence host responses to tumors and may adversly influence responses to immunotherapy. The expression of tumor associated antigens by autologous human primary and metastatic sarcomas has been clearly defined using a panel of monoclonal antibodies. It has been demonstrated that primary tumors and their metastases express similar antigens but almost invariably, micro-heterogeneity of tumor antigen expression results from antigen absent populations of cells within each tumor. The mechanism of heterogeneity for tumor antigen expression of the B16 melanoma system has been defined using a tumor specific monoclonal antibody. Variation in antigen expression correlated with variations of tumor cell density in culture. Monoclonal antibodies have been produced that recognize antigens newly expressed by NIH 3T3 fibroblasts transfected with oncogenes from human tumors. These experiments define a new technique for the production of anti-tumor monoclonal antibodies and will also be useful in defining the mechanism of oncogene-related transformation. We have identified an immunoregulatory factor produced by a variety of human tumors that inhibits in vitro cell mediated immune responses. A murine melanoma that produces an immunosuppressive glycoprotein has also been identified and the glycoprotein has been characterized and purified. The in vivo immunosuppressive effects of murine melanoma derived glycoprotein have been demonstrated. A factor has been isolated from a variety of human tumors that inhibits thymidine incorporation by proliferating tumor cells and also inhibits tumor cell growth. The factor has been purified to homogeneity and the mechanism of its action has been determined. We are currently evaluating interactions between various modalities of immunotherapy to develop new techniques for the treatment of metastatic tumors.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 06656-03 SURG

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Definition and Modification of Neoplastic Tissue Sterol Metabolism

PRINCIPAL INVESTIGATOR *(List other professionel personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	P.D. Schneider	Senior Investigator	SURG	NCI
Others:	S.B. Edge	Medical Staff Fellow	SURG	NCI
	D.A. Potter	Medical Staff Fellow	SURG	NCI
	J.M. Skibber	Medical Staff Fellow	SURG	NCI
	C.M. Gorschboth	Medical Technologist	SURG	NCI

COOPERATING UNITS *(if any)*

Molecular Disease Branch, NHLBI

LAB/BRANCH

Surgery Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0		

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Lipoprotein metabolism in normal human liver, the livers of patients with hereditary hyperlipidemias, and certain human hepatoma lines is being studied in serum-free culture systems. Work previously initiated with liposome interaction with melanoma cells has been expanded because of interesting information about non-specific lipid uptake and, in particular, lipid vesicle uptake by tumor cells. Careful categorization of in vitro responses has been extrapolated to in vivo systems for the first time. Several parameters which make liposomes theoretically practical in limited situations are being elucidated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 06657-02 SURG

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 charecters or less. Title must fit on one line between the borders.)*

Studies to Identify a Circulating Factor that Causes Cachexia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I. J.A. Norton, M.D., Acting Head, Surgical Metabolism Section, SURG NCI
Others: J. Moley, M.D., Medical Staff Fellow, SURG NCI
T. Lawrence, M.D., Expert, SURG NCI
R. Inculet, M.D., Visiting Associate, SURG, NCI

COOPERATING UNITS *(if any)*

Seoras Morrison, Ph.D., Laboratory of Theoretical Biology, NCI NIH

LAB/BRANCH

Surgery Branch

SECTION

Surgical Metabolism Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0		

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

An in vitro assay for muscle proteolysis has been developed. Test sera from normal, septic, and cachectic animals have demonstrated that septic and cachectic animals' sera carry a factor or factors which increases muscle proteolysis.

Sarcoma patients have been studied with intravenous glucose tolerance tests and have been shown to be glucose intolerant (1). Exogenous insulin has been administered to rats bearing sarcomas. Insulin given to tumor bearing animals increases spontaneous food intake, nitrogen balance, body weight gain, and does not promote tumor growth. However, survival studies show no advantage to the insulin treated animals (2).

We have characterized the effects of tumor mass by creating an artificial tumor model that simulates the mass characteristics of our fisher rat sarcoma tumor system (3,4). We know that cachexia is sarcoma dependent in our animal system, because if we remove the tumor, we can totally reverse the cachexia. We have data in parabiotic animal tumor systems that indicates that the sarcoma secretes a factor which mediates the anorexia and body weight loss seen in cachexia. If experiments continue to show that a tumor factor mediates metabolic derangements, we will attempt to describe and isolate the factor.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06658-02 SURG

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Studies of the Pineal Gland Hormone Melatonin and Breast Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: D.N. Danforth, Jr. Senior Investigator SURG NCI

COOPERATING UNITS *(if any)*
Medicine Branch

LAB/BRANCH
Surgery branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	No support staff

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The role of the pineal gland hormone melatonin in the regulation of estrogen receptor (ER) activity and the growth of MCF-7 human breast cancer cells is being studied in vitro and in vivo. We have shown that melatonin rapidly increases the cytosocil and nuclear estrogen receptor activity of human breast cancer cells, a process which is dependent upon protein synthesis. We have also shown that melatonin will increase the ER activity of normal hamster uterine activity in vivo and in vitro in an analogous manner. We are presently studying the mechanism of this induction, and the physiochemical changes in the receptor which accompany induction, including sedimentation properties on sucrose gradients, molecular weight changes by PAGE and salt extraction properties. We are studying the binding of melatonin induced ER to DNA, and to nucleoacidic protein acceptor sites, and are also analyzing the effect of ER induction on growth of MCF-7 cells in vitro and MCF-7 solid tumors in vivo. These studies will further define the importance of melatonin in the regulation of hormone dependent breast cancer. We are also studying the secretion of plasma melatonin in women with hormone dependent breast cancer, women at high risk for breast cancer, and normal subjects. We have found a highly significant inverse correlation between the plasma level of melatonin and the quantity of estrogen or progesterone receptor in human breast cancer. This correlation is independent of age, menopausal status, stage of disease, or plasma levels of steroid hormones. We are studying the plasma melatonin diurnal rhythm in women at high risk for breast cancer in normal subjects to determine whether this abnormality of melatonin secretion precedes, or is a consequence of, breast cancer. Preliminary studies suggest plasma melatonin may be an important factor in determining the estrogen receptor content of human breast cancer.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06659-02 SURG

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Studies of Urologic Malignancy

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: W. Marston Linehan, M.D., Head, Urologic Oncology Section, SURG, NCI

COOPERATING UNITS *(if any)*

Arthur Santora, Metabolic Disease Branch, NIADDK

John Termine, NIDR

LAB/BRANCH
Surgery Branch

SECTION
Urologic Oncology Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2	1	1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In the Urologic Oncology Section of the Surgery Branch the effect of estrogen, LHRH and 5 alpha reductase inhibitors on prostate carcinoma are being evaluated. We also have described and characterized a model for humoral hypercalcemia in nude mice bearing a prostate carcinoma. This is the first description of a model for humoral hypercalcemia for prostate carcinoma. We have also found the hypercalcemic effect to be present in a number of other human prostate carcinomas in nude mice and nude rats. This indicates that the humoral hypercalcemia may be a more generalized effect of the tumor and not localized to the initial cell line in which the effect was observed. We have identified a parathyroid hormone-like factor which is produced by these prostate carcinoma cell lines and we are in the process of characterizing this factor. We have established the presence of bone resorptive activity in prostate carcinoma of tumor extracts and also in the conditioned media from prostate carcinoma cell lines. We are comparing this activity with that found in the hypercalcemia of malignancy seen with hypernephroma tumors. We have also identified an osteoblastic factor which is produced by the prostate carcinoma in tissue culture, i.e. the fact that the tumor-conditioned media stimulates thymidine and proline incorporation by the osteoblastic cell lines. We are in the process of further characterization of the substance, its effect on both osteosarcoma cell lines and human osteoblasts as well as its specificity for human bones and osteoblast precursors.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06660-01

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Study of Immune Adjuvants in Rodent Tumor Models

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: A.E. Chang, M.D. Senior Investigator SURG NCI

Other: Cornelia L. Hyatt, Biologist, SURG, NCI
Hilda Wexler, Biologist, SURG, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Surgery Branch

SECTION
Tumor Immunology Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.5	1.5	2.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This laboratory is involved in defining the in vivo biologic effects of immune enhancing reagents in rodent models. In particular, the administration of interleukin-2 (IL-2), an immunoenhancing lymphokine, is being investigated in murine and rat models to establish rational approaches to the immunotherapy of cancer. The bioavailability, toxicity, immune effects and antitumor effects of IL-2 are being examined in these models. IL-2 administration in conjunction with other immune adjuvants (i.e. immune cells, biological response modifiers) is also being investigated in the treatment of the tumor-bearing host.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 06661-01 SURG

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Immunologic Studies in Patients with Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: M.T. Lotze, M.D. Senior Investigator SURG NCI

Other: Leslie W. Frana, Microbiologist, SURG, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Surgery Branch

SECTION

Tumor Immunology Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.0	1.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Our laboratory's major effort is the development and evaluation of immunologic reagents in patients with malignancy. Preparation of single cell suspensions from human tumors and evaluation and dervation of cloned and bulk populations of autologous lymphocytes reactive to them are a major goal. The effort was begun in the last eighteen months and over 100 tumor preparations have been evaluated. Over 40 mixed lymphocyte tumor interactions have been carried out and evaluated. Over twenty different individuals have had cloning carried out on the sensitized cells.

In addition to investigation of cellular interactions with tumor, we have carried out an active program in investigation of the in vivo role of interleukin-2. In addition to carrying out preliminary toxicity and biologic evaluations of human IL-2 in rodents extensive in vitro evaluations of murine effects of both tumor derived and recombinant IL-2 have been carried out in the laboratory.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09200-04 BTB

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Phase I Trials of Recombinant and Nonrecombinant Interferons in Cancer Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	K. A. Foon	Head, Clinical Investigations Section	BRMP, NCI
Others:	P. B. Abrams	Expert	BTB, NCI
	G. C. Bottino	Medical Staff Fellow	BTB, NCI
	M. F. Fer	Visiting Scientist	BTB, NCI
	H. C. Stevenson	Senior Investigator	BTB, NCI
	R. B. Herberman	Acting Associate Director	BRMP, NCI

COOPERATING UNITS *(if any)* Hoffmann-La Roche, Inc., Nutley, NJ; Burroughs-Wellcome Co., Research Triangle Park, NC; NCI-FCRF; Genentech, Inc., San Francisco, CA; Immunomodulatory Laboratories, Houston, TX; Meloy Laboratories, Springfield, VA

LAB/BRANCH

Biological Therapeutics Branch

SECTION

Clinical Investigations Section

INSTITUTE AND LOCATION

NCI-FCRF, Frederick, MD 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	2.0	2.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Various recombinant and nonrecombinant α and γ interferons have been tested in Phase I trials in cancer patients in order to study the toxicity, antitumor effects, immunomodulatory effects and pharmacokinetics of these preparations. The initial Phase I trials employed highly purified recombinant leukocyte A interferon and human Namalva cell lymphoblastoid interferon and have been previously reported. We have recently completed 3 phase I studies with recombinant and nonrecombinant γ interferons. Toxicity for each of these preparations was similar to α interferons with a flu-like syndrome as well as minor hematologic toxicity, primarily decreased leukocytes. Dose-dependent serum levels were measured using both a biologic assay and enzyme-linked immunosorbent assay for the recombinant γ interferon. No antitumor responses were seen.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 09233-03 BTB

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Trials Recomb. Leukocyte IF in Pts. w/Lymphoproliferative Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	K. A. Foon	Head, Clinical Investigations Section	BTB, NCI
Others:	H. C. Stevenson	Senior Investigator	BTB, NCI
	P. B. Abrams	Expert	BTB, NCI
	M. F. Fer	Visiting Scientist	BTB, NCI
	R. B. Herberman	Acting Associate Director	BRMP, NCI

COOPERATING UNITS *(if any)*

Hoffmann-La Roche, Inc., Nutley, NJ; NCI-FCRF; NCI-Navy MOB, NCI; POB, NCI; MB, NCI

LAB/BRANCH

Biological Therapeutics Branch

SECTION

Clinical Investigations Section

INSTITUTE AND LOCATION

NCI-FCRF, Frederick, MD 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.0	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In our Phase I trial of recombinant leukocyte interferon (1981-82) in patients with a variety of disseminated cancers, we demonstrated that this agent could be administered up to doses of 50 x 10 to the sixth power/meter squared i.m. 3 times weekly without unacceptable toxicity. This trial also showed objective evidence of antitumor response (partial remissions) in some patients with non-Hodgkin's lymphoma, breast cancer, chronic lymphocytic leukemia and Hodgkin's disease. Immunologic monitoring of patients receiving this agent failed to reveal any dose-dependent immunologic effect which correlated with tumor response. It was therefore decided to initiate a Phase II efficacy trial of recombinant leukocyte interferon at a maximum tolerated dose, with dose reductions as necessary for unacceptable toxicity. Phase II efficacy trials were initiated in patients with various lymphoproliferative disorders, including non-Hodgkin's lymphoma, chronic lymphocytic leukemia and cutaneous T-cell lymphoma, as well as patients with refractory metastatic breast cancer. Eighteen patients with metastatic breast cancer were treated in 1982 with recombinant leukocyte A interferon, with 16 patients progressing while on therapy and 2 remaining stable. Eighty-four patients with a variety of lymphomas have been treated, with a 56% response rate in 24 patients with favorable-histology lymphoma (9 partial responses, 4 complete responses) and a 48% response rate in 19 patients with cutaneous T-cell lymphoma (9 partial responses). Only 2 of 19 patients with chronic lymphocytic leukemia and 3 of 16 patients with unfavorable-histology lymphoma responded.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09235-03 BTB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Phase I Trials of Antitumor Monoclonal Antibodies in Patients with Cancer

PI:	K. A. Foon	Head, Clinical Investigations Section	BRMP, NCI
Others:	P. G. Abrams	Expert	BTB, NCI
	G. C. Bottino	Medical Staff Fellow	BTB, NCI
	A. C. Morgan	Acting Head, MoAb/Hybridoma Section	BTB, NCI
	R. B. Herberman	Acting Associate Director	BRMP, NCI
	H. C. Stevenson	Senior Investigator	BTB, NCI
	M. F. Fer	Visiting Scientist	BTB, NCI
	R. W. Schroff	Senior Staff Fellow	BTB, NCI
	C. S. Woodhouse	Visiting Fellow	BTB, NCI

COOPERATING UNITS *(if any)*
NCI-FCRF; NCI-Navy MOB, NCI; MB, NCI

LAB/BRANCH
Biological Therapeutics Branch

SECTION
Clinical Investigations Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, MD 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.0	2.5	2.5

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Monoclonal antibodies reactive with various human tumor cells have been prepared from murine hybridomas according to standard techniques. Phase I trials of antitumor monoclonal antibodies initiated by the Clinical Investigations Section include studies of anti-T cell monoclonal antibodies in patients with chronic lymphocytic leukemia (CLL) and cutaneous T cell lymphoma (CTCL), anti-melanoma monoclonal antibody in patients with disseminated melanoma, and anti-idiotype monoclonal antibody in patients with malignant lymphoma and CLL. We have treated 13 patients with CLL and 12 patients with CTCL with the T101 monoclonal antibody. We have witnessed transient reductions in circulating leukemia cells but have not seen reductions in the size of enlarged organs or lymph nodes. Five patients with CTCL had minimal improvement in their skin lesions. Toxicity has included mild fever and minimal shortness of breath. Twenty patients with metastatic melanoma have been treated with an antibody to a 250,000 m.w. melanoma associated antigen. While we have seen no reductions in the size of metastatic lesions, we have seen excellent in vivo localization of antibody in cutaneous lesions. We have also successfully imaged patients by radionuclide scans using 111Indium-T101 and 111Indium-9.2.27. We have successfully developed anti-idiotype antibodies for 4 patients with B-cell lymphomas and one with CLL. We have begun therapy on the patient with CLL and expect to begin therapy for at least 2 other patients by summer 1984.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09258-02 BTB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Trial of Plasma Perfused Over Immobilized Protein A in Patients with Breast Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. F. Fer	Visiting Scientist	BTB, NCI
Others:	H. C. Stevenson	Senior Investigator	BTB, NCI
	K. A. Foon	Head, Clinical Investigations Section	BTB, NCI
	J. S. Beman	Nurse Specialist	BTB, NCI
	R. B. Herberman	Acting Associate Director	BRMP, NCI
	R. K. Oldham	Associate Director (until 1/84)	BRMP, NCI
	J. W. Pearson	Microbiologist	BTB, NCI

COOPERATING UNITS *(if any)*
NCI-FCRF; Baylor College of Medicine, Houston, Texas

LAB/BRANCH
Biological Therapeutics Branch

SECTION
Clinical Investigations Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, MD 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	2.5	0.5

CHECK APPROPRIATE BOX(ES)

- [x] (a) Human subjects
- [ ] (b) Human tissues
- [ ] (c) Neither
- [ ] (a1) Minors
- [x] (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The goal of this project is to explore the therapeutic potential and biological effects of autologous plasma perfused over protein A in patients with breast cancer. Patients with recurrent measurable breast cancer and good performance status are treated with previously stored autologous plasma perfused over protein A immobilized on charcoal collodion. The dose of protein A and the quantities of plasma perfused are escalated in a stepwise fashion depending on the patient's tolerance. The patients are closely observed for evidence of objective tumor regression, inflammatory changes around the lesions, toxicity, and immune modulation. Seven patients have undergone 11 courses of therapy to date. Some patients have experienced tumor pain following plasma therapy but there have been no objective tumor regressions. Animal studies performed by direct injections of protein A in three animal tumor models have not shown any antitumor effects. In vitro studies have been performed to explore the antiproliferative and anticlonogenic effects of protein A in the presence of human serum (complement) and/or a monoclonal antibody recognizing an antigen expressed by the cultured tumor cells. Although protein A may exert some complement-dependent effect to reduce colony growth in the clonogenic assay system, there has been no synergistic cytotoxicity with the monoclonal antibody in these preliminary in vitro experiments.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09276-01 BTB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Phase I Trial of Poly ICLC in Cancer Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	K. A. Foon	Head, Clinical Investigations Section	BTB, NCI
Others:	P. G. Abrams	Expert	BTB, NCI
	H. C. Stevenson	Senior Investigator	BTB, NCI
	M. F. Fer	Visiting Scientist	BTB, NCI
	G. C. Bottino	Medical Staff Fellow	BTB, NCI
	R. B. Herberman	Acting Associate Director	BRMP, NCI

COOPERATING UNITS *(if any)*
NCI-FCRF; Portsmouth Naval Medical Center

LAB/BRANCH
Biological Therapeutics Branch

SECTION
Clinical Investigations Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, MD 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	1.5	1.5

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have entered 20 patients with a variety of metastatic solid tumors on the twice weekly IV dose of 1 mg/meter squared and 4 mg/meter squared of the interferon inducer poly ICLC. We have not demonstrated an antitumor effect in any patient and have witnessed toxicity that included mild fevers, fatigue, nausea, and mild hypotension. Interferon levels have been measured in all patients studied and are consistently higher in patients treated with 4 mg/meter squared. Immunologic monitoring has demonstrated a consistent enhancement of monocyte-mediated cytostasis, depression of mitogen-stimulated proliferative responses in vitro, and decreased or no change in natural killer activity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09278-01 BTB

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Gene Expression Studies Performed on Hu Monocytes: Potential Clin Applications

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	H. C. Stevenson	Senior Investigator	BTB, NCI
Others:	P. J. Miller	Biologist	BTB, NCI

COOPERATING UNITS *(if any)*

Ingene Laboratories, Santa Monica, CA; Neurobiology Branch, Johns Hopkins University, Baltimore, MD

LAB/BRANCH

Biological Therapeutics Branch

SECTION

Clinical Investigations Section

INSTITUTE AND LOCATION

NCI-FCRF, Frederick, MD 21701

TOTAL MAN-YEARS	PROFESSIONAL:	OTHER
1.0	.5	.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Human monocytes have been employed in in vitro assay systems to determine the macromolecular basis for their function. Monocytes have been studied in their unactivated state, following muramyldipeptide activation, and following activation with poly IC/LC; unactivated cells neither release interferon nor fibroblast growth factor, muramyldipeptide stimulates monocytes to release enhanced amounts of fibroblast growth factor, and poly IC/LC only stimulates interferon production by human monocytes. When the messenger RNA from these three distinct activation states of human monocytes was analyzed for α-interferon gene expression, unactivated monocytes were found not to synthesize interferon messenger RNA. In contrast, poly IC/LC-stimulated monocytes synthesize three molecular weight forms of the interferon message at 1.0 kb, 2.5 kb, and 7.5 kb. Muramyldipeptide-stimulated monocytes synthesize only a 2.5 kb interferon messenger RNA; the synthesis of this message appears to be associated with an intracytoplasmic form of interferon activity. This technology has potential clinical application for monitoring the gene expression events associated with BRM administration in cancer patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09279-01 BTB

PERIOD COVERED

October 31, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Phase I Trials of Interleukin 2 in Patients with Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	H. C. Stevenson	Senior Investigator	BTB, NCI
Others:	K. Foon	Head, Clin. Investigations Section	BTB, NCI
	P. Abrams	Expert	BTB, NCI
	F. Ruscetti	Acting Head, Lymphokines Section	LMI, NCI
	P. Sugarbaker	Senior Investigator	SB, NCI
	A. Maluish	Senior Investigator	BTB, NCI
	E. McClamrock	Head Nurse	BTB, NCI
	R. Herberman	Acting Associate Director	BRMP, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Biological Therapeutics Branch

SECTION

Clinical Investigations Section

INSTITUTE AND LOCATION

NCI-FCRF, Frederick, MD 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4	3	1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A clinical trial investigating the potential role of interleukin 2 in the treatment of patients with cancer has been designed. This trial will test the toxicity of both natural and recombinant interleukin 2 preparations when given subcutaneously, intraperitoneally, intravenously (slow or by i.v. push), or intramuscularly in escalating doses. Concomitantly, we will study the pharmacokinetics and immunomodulatory dose properties of both recombinant and natural interleukin 2 when given by these five routes in escalating doses. Finally, in an attempt to evaluate the possible antitumor effects of interluekin 2 in cancer patients, we will administer the agent for three weeks on a daily basis at either the optimal immunomodulatory dose (as determined by our in vitro immunomonitoring assays), at one tenth of the optimal immunomodulatory dose, or at 10 times the optimal immunomodulatory dose, provided that this dose is below the maximum tolerated dose (defined from previous toxicity testing).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 09280-01 BTB

PERIOD COVERED

October 1, 1983 to September 39, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Characterization of Elutriator-Purified Human Monocytes: Clinical Applications

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	H. C. Stevenson	Senior Investigator	BTB, NCI
Others:	P. Miller	Biologist	BTB, NCI
	J. Beman	Research Nurse Specialist	BTB, NCI
	K. Foon	Head, Clin. Investigations Section	BTB, NCI
	P. Sugarbaker	Medical Officer	SB, NCI
	S. Larson	Medical Officer	NM, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Biological Therapeutics Branch

SECTION

Clinical Investigations Section

INSTITUTE AND LOCATION

NCI-FCRF, Frederick, MD 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5	3	2

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Human monocytes have been removed from the peripheral blood of normal volunteers and cancer patients for study in a wide range of immunologic assay systems. The technique of countercurrent centrifugal elutriation has been applied to these cells to generate as many as 10 to the 9th power 95% pure cells. In addition, lymphocytes that are completely monocyte-depleted can be obtained by the same technology. Elutriation generates cells that are in suspension; we have developed techniques to maintain these cells in suspension culture using serum-free media and specially developed Teflon labware. Thus, these cells are thought to be most representative of the native state of monocytes in the bloodstream. These cells have been studied with regard to their accessory cell functions for human lymphocytes, their MIF activity and chemotactic activity, their ability to release biological response modifiers (including colony stimulating factor, interferon, fibroblast growth factor, prostaglandins and soluble cytotoxic factors); in addition, the tumoricidal activity of these cells in antibody-dependent cellular cytotoxicity and spontaneous cytotoxicity assay systems has been measured. Having documented the tumoricidal activity of elutriator-purified monocytes, we have initiated attempts to utilize large numbers of these cells in an adoptive transfer setting in patients with peritoneal carcinomatosis; these patients received weekly administration of their own elutriator-purified monocytes (activated with γ-interferon) into their peritoneal cavity via an indwelling Tenckhoff catheter.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09210-04 BTB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Molecular, Serologic, and Biologic Characterization of the 250 Kd MAA

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: A. C. Morgan, Jr. Acting Head, MoAb/Hybridoma Section BTB, NCI

Others: C. S. Woodhouse Visiting Fellow BTB, NCI

COOPERATING UNITS *(if any)*
Brain Cancer Research Fund, Frenchay Hospital, Briston, England (P. M. Allan, M.D.)

LAB/BRANCH
Biological Therapeutics Branch

SECTION
Monoclonal Antibody/Hybridoma Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, Maryland 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Molecular, serologic and functional approaches were utilized for the characterization of a monoclonal antibody to a human melanoma-associated 250 Kd glycoprotein-proteoglycan complex. The rationale for these studies was that it is necessary to understand antibody-antigen systems in order to optimize the therapeutic and diagnostic usefulness of monoclonal antibodies. The 259 Kd MAA, previously thought to be melanoma-specific, was detected on certain brain tumors in addition to cerebral metastases of melanoma but not on normal brain tissues. The antibody appears to have considerable diagnostic potential for brain tumors as well as melanoma. An important finding for therapeutic use of the antibody was that reactivity of antibody 9.2.27 to fresh human melanoma cells was characterized by high antigen density compared to other human MAA and a low degree of heterogeneity. This was shown to be dependent on the epitope recognized by a monoclonal antibody; other antibodies to the 250 Kd MAA reacted less well and gave a higher degree of heterogeneity on tissue sections and single cell suspensions. Preliminary data indicate that the 250 Kd MAA is functionally related to α_2-macroglobulin and can bind proteases. These studies are continuing to pursue means of characterization of this melanoma-associated antigen with regard to tumor cell biology and therapeutic application.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09226-04 BTB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Preclinical Evaluation of MoAb Therapy Against Established Tumors and Metastases

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. W. Pearson	Microbiologist	BTB, NCI
Others:	A. C. Morgan, Jr.	Acting Head, MoAb/Hybridoma Section	BTB, NCI
	G. Pavanasasivam	Visiting Scientist	BTB, NCI
	M. Fer	Visiting Scientist	BTB, NCI
	C. Woodhouse	Visiting Fellow	BTB, NCI
	A. I. Alarif	Visiting Scientist	BTB, NCI

COOPERATING UNITS *(if any)*
Laboratory of Biochemistry, NCI, NIH (W. Evans); Program Resources, Inc. (B. Bohn); Hybritech, Inc., LaJolla, CA (G. David).

LAB/BRANCH
Biological Therapeutics Branch

SECTION
Monoclonal Antibody/Hybridoma Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, MD 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.5	1.5	2.0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Several types of monoclonal antibodies (MoAb) with toxins have been under evaluation in two animal models: 1) the L10 hepatocellular carcinoma in syngeneic guinea pigs in which the conjugates were assessed against both primary and metastatic tumors and 2) a human melanoma in nude mice. Emphasis in these investigations involved determining optimal therapeutic doses of the immunoconjugates and single versus multiple treatments against established tumors and spontaneous metastasis. Immunoconjugate preparations of abrin (400-1120 µg's) and ricin (500 µg's) A chains conjugated to D3 MoAb significantly delayed the growth of established L10 tumors and retarded the development of spontaneous axillary metastasis in guinea pigs. A single I.V. administration of a gelonin - D3 conjugate (100 µg) significantly inhibited L10 tumor growth for up to 1 week. However, there was no effect on the development of axillary metastasis. A 9.2.27 MoAb reactive with a human melanoma either delayed or completely suppressed tumor growth in the prepalpable model, depending on the size of the original tumor inoculum in nude mice. In contrast, unconjugated MoAb had little or no effect on established palpable tumors. However, a 9.2.27 abrin A chain or gelonin conjugate significantly retarded the growth of established tumors. These studies are designed to give information for clinical trials with immunoconjugates.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09236-03 BTB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Develop. of Hu T-Cell Hybridoma, Monocyte-Macrophage Hybridomas & LGL Hybridomas

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	K. A. Foon	Head, Clinical Investigations Section	BTB,	NCI
Others:	R. W. Schroff	Senior Staff Fellow	BTB,	NCI
	P. G. Abrams	Expert	BTB,	NCI
	J. R. Ortaldo	Biologist	BTB,	NCI
	R. B. Herberman	Acting Associate Director	BRMP,	NCI
	H. C. Stevenson	Senior Investigator	BTB,	NCI
	E. S. Kleinerman	Senior Investigator	BTB,	NCI
	F. W. Ruscetti	Acting Head, Lymphokines Section	LMI,	NCI

COOPERATING UNITS *(if any)*
NCI-FCRF

LAB/BRANCH
Biological Therapeutics Branch

SECTION
Monoclonal Antibody/Hybridoma Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, MD 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1	.5	.5

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The human macrophage line U937 and the human T-lymphoblastoid line HSB2 have been rendered sensitive to hypoxanthine-aminopterin-thymidine (HAT) culture medium by treatment with 8-azaguanine. The HSB2 cell line was fused to T lymphocytes that were stimulated with concanavalin A for 48 hours. Hybridomas were generated that constitutively produced interleukin 2 and chemotactic factor. Eight of these hybridomas have been cloned and continue to constitutively secrete (>12 months) interleukin 2 in concentrations from 2 to 40 times that of an equal number of mitogen-stimulated peripheral blood lymphocytes. One clone also produces monocyte chemotactic factor and other lines produce fibroblast activating factor. Fusion of the U937 line with purified human monocytes has not led to successful clones. However, fusion of human monocytes to the murine myeloma line 653 led to stable human-mouse hybridomas with twice the DNA content of the parent 653 line. The characteristics of these hybridomas and their secretory products are currently being investigated.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09237-03 BTB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Murine Monoclonal Antibodies to Human Leukocytes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	K. A. Foon	Head, Clinical Investigations Section	BTB, NCI
Others:	H. C. Stevenson	Senior Investigator	BTB, NCI
	E. S. Kimball	Acting Head, Biochemistry Section	LMI, NCI
	R. W. Schroff	Senior Staff Fellow	BTB, NCI

COOPERATING UNITS *(if any)*
NCI-FCRF; LCI, NIAID

LAB/BRANCH
Biological Therapeutics Branch

SECTION
Monoclonal Antibody/Hybridoma Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, MD 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1	.5	.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have developed a series of monoclonal antibodies to human granulocytes, monocytes, platelets, and eosinophils. An IgG1 monoclonal antibody (PMN70) produced against human granulocytes reacted specifically with mature granulocytes and did not react with any other normal circulating or bone marrow cells. No reactivity was found when this antibody was tested with a series of fresh leukemia cells or leukemia cell lines. Immunoprecipitation of the antigen identified by this antibody demonstrated a 70,000 dalton protein. Another monoclonal antibody, also an IgG1, produced against human monocytes (Mo95), reacted with human granulocytes, monocytes, eosinophils, and large granular lymphocytes. This antibody reacted with myeloid precursor cells in the bone marrow and reacted with a small proportion (20%) of the acute myelogenous leukemia cells tested. The molecular weight of the antigen identified by this antibody was 95,000 daltons. A series of monoclonal antibodies produced against human platelets were isotyped as IgG1, IgM and IgG2a. One of these antibodies appeared to react with platelets and granulocytes while the other two reacted exclusively with platelets and no other circulating normal cells. Further characterization of these antibodies, including the molecular characterization of the antigens they react with and their effect on platelet function, is ongoing. An IgG1 monoclonal antibody has been produced against human eosinophils (Eo1). This antibody also reacted with monocytes, granulocytes, and myeloid precursor cells in the bone marrow. This antibody immunoprecipitated a 95,000 dalton protein.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09238-03 BRB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Monoclonal Antibodies Against Bronchogenic Carcinoma

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P.G. Abrams	Expert	BTB, NCI
Others:	A.C. Morgan, Jr.	Acting Head, MoAb/Hybridoma Section	BTB, NCI
	C.S. Woodhouse	Visiting Fellow	BTB, NCI
	M.F. Fer	Visiting Scientist	BTB, NCI
	E. Kimball	Acting Head, Biochemistry Section	LMI, NCI
	A.R. Wilt	Biol. Lab. Tech.	BTB, NCI
	T.A. Gregorio	Biol. Lab. Tech.	BTB, NCI

COOPERATING UNITS *(if any)*
Program Resources, Inc. (K. Hwang)

LAB/BRANCH
Biological Therapeutics Branch

SECTION
Monoclonal Antibody/Hybridoma Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, MD 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Monoclonal antibodies (MA) directed against tumor-associated antigens in bronchogenic carcinomas would be useful for early diagnosis of non-small cell tumors, that may then be surgically cured, or for the treatment of micrometastatic disease. Although a number of such antibodies have been reported, few have promise as therapeutic reagents due to lack of surface membrane expression or undesirable isotype (IgM) that may not adequately diffuse into extravascular spaces. We have produced and characterized one MA (503D8) that reacts with a surface membrane antigen of 15,000 daltons that is also secreted into cell culture supernatants. Immunoperoxidase staining of human tissues revealed markedly enhanced expression of the antigen in lung tumors compared with normal lung but sufficient expression in liver and kidney to render it unattractive as a therapeutic reagent. Another MA (353 H10), however, reacts predominantly with squamous cell carcinomas of the lung and displays only very minor reactivity with normal tissue (occasional distal tubules of kidney).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09239-03 BTB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Human Monoclonal Antibodies Against Tumor Associated Antigens

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Paul G. Abrams	Expert	BTB, NCI
Others:	A. C. Morgan, Jr.	Acting Head, MoAb/Hybridoma Section	BTB, NCI
	S. Wilburn	Biologist	LMI, NCI
	S. Pickeral	Biologist	LMI, NCI

COOPERATING UNITS *(if any)*
Program Resources, Inc. (J.A. Rossio, H.C. Kager).

LAB/BRANCH
Biological Therapeutics Branch

SECTION
Monoclonal Antibody/Hybridoma Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, MD 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Human monoclonal antibodies (HMA) may not only demonstrate which antigens are immunogenic in the host, but also may be useful for prolonged MA therapy when murine antibodies have elicited antiglobulin responses to the Fc region. We have demonstrated that stable, HMA-secreting clones may be produced with various human myeloma cell lines, but that the efficiency of this process is low. We have also demonstrated that HMA-secreting hybrids between human lymphocytes and mouse myelomas may be grown in the peritoneal cavities of nude mice to produce highly concentrated human immunoglobulins. Although we developed an in vitro model system to stimulate human lymphocytes prior to cell fusion for HMA production utilizing tetanus toxoid as a model antigen, this has not as yet been successfully applied to tumor antigens. Current work is focused on isolating B-cells with surface membrane antibody directed at the 250 Kd melanoma associated antigen and then expanding these lymphocytes in B-cell growth factor (BCGF) prior to fusion.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09253-02 BTB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Development of Immunoconjugates for Cancer Therapy and Diagnosis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	A. C. Morgan, Jr.	Acting Head, MoAb/Hybridoma Section	BTB, NCI
Others:	J. W. Pearson	Microbiologist	BTB, NCI
	G. Pavanasasivam	Visiting Fellow	BTB, NCI
	A. Alarif	Visting Scientist	BTB, NCI
	R. Oldham	Associate Director (until 1/84)	BRMP, NCI

COOPERATING UNITS *(if any)*
Program Resources Inc., FCRF-NCI (K.M. Hwang); Nuclear Medicine Department, NIH (A. Keenan)

LAB/BRANCH
Biological Therapeutics Branch

SECTION
Monoclonal Antibody/Hybridoma Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, MD 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.5	1.0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A series of immunconjugates have been prepared consisting of several types of toxins and drugs conjugated to anti-melanoma antibody 9.2.27, and the D3 antibody to L10 hepatocellular carcinoma. 9.2.27 formed potent (ID_{50}=10^{-4}-10^{-13} M) immunoconjugates with intact abrin and ricin, gelonin, pokeweed antiviral protein (PAP) and the A chains of ricin and abrin. These are the most potent conjugates yet reported in the literature. Immunotoxins of 9.2.27 were highly selective, killing antigen positive cells at concentrations between 1000 to 50,000 times less than antigen negative cells. D3 conjugates of gelonin, PAP, ricin and abrin A chains varied in potentency from 10-9 to 10-11. D3 conjugates with whole abrin, however, were reproduciably more toxic at 10^{-12} to 10^{-13} (ID_{50}) and still retained a selectivity of 100 to 1000 fold.

Within the last 4 months of the fiscal year, Dr. Alarif has undertaken the conjugation of the chemotherapeutic drugs emthotrexate adriamycin, and bleomycin. A general ligand system has been developed using a poly-lysine-drug linker conjugated by disulfide linkage to antibody. Bleomycin conjugtes have been found to be the most potent ($3X10^{-8}$ M ID_{50}), similar to levels of toxicity of free drug.

Our evaluation of toxin conjugates in animals against established palpable tumors had indicated we could almost completely inhibit tumor growth.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09270-01 BTB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Homologues of Serum Proteins Synthesized by Melanoma Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: A. C. Morgan, Jr. Acting Head, MoAb/Hybridoma Section BTB, NCI

Others: None

COOPERATING UNITS *(if any)*

LAB/BRANCH
Biological Therapeutics Branch

SECTION
Monoclonal Antibody/Hybridoma Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, MD 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A novel approach has been used to produce monoclonal antibodies to tumor-associated antigens which may be of value for immunodiagnosis or prognosis of human tumors. We have established that human melanoma cells synthesize proteins that are serologically homologous but not molecularly identical to normal serum constituents. We have detected several such proteins in spent culture medium of human melanoma cells but have initially concentrated on α_2-macroglobulin, a wide-spectrum protease inhibitor. We have demonstrated synthesis, characterized the molecular form, and produced monoclonal antibodies to this tumor cell product. We are presently using immunization methods with insolubilized immune complexes to produce further monoclonal antibodies which may recognize molecular differences between the melanoma and serum forms of the α_2-macroglobulin. This methodology should produce a new category of monoclonal reagents which may not only be clinically useful but also may help to elucidate the functional roles of these homologous serum proteins.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09271-01 BTB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
MAA: Biological, Biochemical Studies on the Clinical Usefulness

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
PI: A. C. Morgan, Jr. Acting Head, MoAb/Hybridoma Section BTB, NCI

Others: None

COOPERATING UNITS *(if any)*
Baylor College of Medicine, Houston, TX (Roger Rossen, M.D.)

LAB/BRANCH
Biological Therapeutics Branch

SECTION
Monoclonal Antibody/Hybridoma Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, MD 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The 100K-dalton human tumor-associated antigen, originally detected in spend culture medium of human melanoma cells, has been characterized biochemically and functionally, and has been preliminarily assessed for utility and immunoprognosis of human melanoma. The rationale for these studies are that this glycoprotein, defined by monoclonal antibody, represented a different class of melanoma antigen than previously described; i.e., it is predominantly secreted rather than expressed at the cell surface and thus offers potential as a serum marker. Serum levels were shown to correlate with tumor burden in melanoma patients. The 100K antigen was shown to also be present in normal serum, at levels of 100 ng/ml or less, complexed in a non-covalent manner with human serum albumin. The presence of normal serum was used to determine the phylogenetic distribution of the tumor marker: the antigen was present in sera and in the spent culture medium of cells from humans and higher apes but not New World monkeys or lower animals, indicating the antigen is a rather late evolutionary development. Preliminary data indicate the 100K MAA may share similarities with C-reactive protein, a primitive immunoglobulin-like acute phase reactant. Studies are continuing to determine its usefulness in diagnosis and prognosis, and possibly its functional role, e.g., its influence on host immune responses.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09272-01 BTB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Production of Monoclonal Antibodies to Human Tumor-Associated Antigens

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	A. C. Morgan, Jr.	Acting Head, MoAb/Hybridoma Section	BTB, NCI
Others:	C. Woodhouse	Visiting Fellow	BTB, NCI
	R. K. Oldham	Associate Director (until 1/84)	BRMP, NCI

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Biological Therapeutics Branch

SECTION
Monoclonal Antibody/Hybridoma Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, Maryland 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.5	2.0	2.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

To increase the efficiency of producing monoclonal antibodies to tumor-associated antigens, we have used immunogens which are: 1) depleted of highly immunogenic non-tumor-associated components, 2) enriched in tumor-associated components, and 3) presented in an immunogenic fashion. Selective peripheral protein extracts from colon adenocarcinoma have been combined with insolubilized lectins. These immunogens, when compared to whole cells or crude membranes, elicited far more hybridomas with specificity to tumor-associated antigens. Unexpectedly, we also found a subclass restriction based upon the lectin used for immunoperoxidase techniques and have found minimal or no normal tissue reactivity but with extensive reactivity to adenocarcinomas of the colon, lung, and breast. These methods have considerable potential for producing monoclonal antibodies which may be useful in therapy and diagnosis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09273-01 BTB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Intracellular Expression of Leukocyte and Tumor-Associated Antigens

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	R. W. Schroff	Staff Fellow	BTB, NCI
Others:	A. C. Morgan, Jr.	Acting Head, MoAb/Hybridoma Section	BTB, NCI
	J. R. Ortaldo	Deputy Head, Natural Immunity Section	BTB, NCI
	H. Young	Senior Investigator	LMI, NCI
	F. Ruscetti	Acting Head, Lymphokine Section	LMI, NCI

COOPERATING UNITS *(if any)*
Program Resources Inc., Frederick Cancer Research Facility, Frederick, MD (R. Klein, B. Carpenter, M. Farrell, R. McIntyre).

LAB/BRANCH
Biological Therapeutics Branch

SECTION
Monoclonal Antibody/Hybridoma Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, Maryland 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.5	2.0	1.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Lysolecithin has been employed as a cell membrane permeabilizing agent to enable rapid and quantitative assessment of internal antigens by immunofluorescence flow cytometry with little or no nonspecific immunofluorescence. Using this technique, we have demonstrated the intracellular expression of several lymphoid and tumor-associated antigens on cells that lack detectable expression of these antigens on the cell surface. Studies are currently in progress to determine the molecular form of the intracellular antigens, the possible biochemical alterations in the antigen as expression changes from intracellular to cell surface, and the regulation of antigen expression by normal and malignant cells. The potential of this technique for monitoring uptake of drug and toxin monoclonal antibody immunoconjugates by normal and malignant cells following therapy with these agents, and the value of this procedure in screening for intracellular antigens such as oncogene products is also under investigation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09274-01 BTB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Immunological Monitoring of Patients Receiving Monoclonal Antibody Therapy

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	R. W. Schroff	Staff Fellow	BTB, NCI
Others:	A. C. Morgan, Jr.	Acting Head, MoAb/Hybridoma Section	BTB, NCI
	K. A. Foon	Head, Clinical Investigations Section	BTB, NCI
	C. S. Woodhouse	Visiting Fellow	BTB, NCI
	S. Wilburn	Biologist	BTB, NCI

COOPERATING UNITS *(if any)*
Program Resources, Inc., FCRF, Frederick, MD (A. Maluish, M. Farrell, R. Klein, and B. Carpenter).

LAB/BRANCH
Biological Therapeutics Branch

SECTION
Monoclonal Antibody/Hybridoma Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, MD 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.5	2.5	2.0

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Patients receiving therapy with the T101, 9.2.27 or anti-idiotype monoclonal antibodies are being examined to assess localization and retention of the monoclonal antibody on the tumor, the pharmacokinetics of the infused antibody, and the immune response of the recipient to the antibody. These studies have demonstrated the ability of these monoclonal antibodies to reach tumor cells in various tissue locations and, with the appropriate dose and schedule of administration, to coat most or all of the tumor cells. Administration of the T101 antibody is accompanied by antigenic modulation which, although undesirable for therapy with monoclonal antibody alone, may provide an efficient means for internalization of immunoconjugates of monoclonal antibodies with drugs, toxins or isotopes. As a part of this project, in vitro studies of antigenic modulation and procedures by which it can be enhanced or inhibited are underway to complement our clinical trials.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09277-01 BTB

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Dev. of Anti-id. Mur. MoAb for Therapy of Pts with B-cell-derived Leu. or Lymph.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	K. A. Foon	Head, Clinical Investigations Section	BTB, NCI
Others:	R. W. Schroff	Senior Staff Fellow	BTB, NCI
	P. G. Abrams	Expert	BTB, NCI
	A. C. Morgan	Acting Head, MoAb/Hybridoma Section	BTB, NCI

COOPERATING UNITS *(if any)*

NCI-FCRF; Damon Biotech, Needham Heights, MA.

LAB/BRANCH

Biological Therapeutics Branch

SECTION

Monoclonal Antibody/Hyrbridoma Secton

INSTITUTE AND LOCATION

NCI-FCRF, Frederick, MD 21755

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.5	1.5	2.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We are investigating optimal procedures for the production of idiotypic immunoglobulin, development of murine monoclonal anti-idiotype antibodies to these immunoglobulins, and evaluating the therapeutic effectiveness of anti-idiotype therapy in patients with B-cell leukemias or lymphomas. It has been possible to produce stable idiotype-secreting heterohybrids by pretreatment of patient tumor cells with 4B-phorbal, 12B-myristate, 13a-acetate (TPA). By growing idiotype-secreting heterohybrids in the peritoneal cavity of nude mice, large quantities of highly concentrated preparations of the patient's idiotypic immunoglobulin have been produced. Anti-idiotype antibodies have been developed for patients with diffuse well-differentiated lymphoma (DWL), chronic lymphocytic leukemia (CLL), and hairy cell leukemia (HCL). Large amounts of anti-idiotype antibodies are being produced for the treatment of the patients with nodular poorly differentiated lymphoma with a relatively low tumor burden. The goal of current laboratory studies will be to formulate a more efficient technology for the development of anti-idiotype monoclonal antibodies.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09228-04 BTB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Further Characterization of Natural Killer (NK) Cells in the Rat

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. W. Reynolds	Senior Staff Fellow	BTB, NCI
Others:	D. Reichardt	Biol. Lab. Tech.	BTB, NCI

COOPERATING UNITS *(if any)*
LCC, NCI-FCRF (J. Ward); IB, DCBD, NCI (P. Henkart); Pfizer Central Research Labs (R. Goldfarb); Karolinska Institute, Sweden (H. Wigzell); REP-Inst. of the Organ. for Health Res. TNO, Netherlands (R. Bolhuis); Univ. of Calif., San Diego (S. Hedrich); Univ. of Calif. Los Angeles (S. Wright).

LABORATORY
Biological Therapeutics Branch

SECTION
Natural Immunity Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, MD 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	0.5	1.0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The present studies have further characterized the natural killer (NK) cell system in rats. Results using a wide variety of target cells have shown that the naturally cytotoxic effector cells for both normal bone marrow and tumor targets are all included in the large granular lymphocyte (LGL) subpopulation; further emphasizing the importance of these cells in controlling bone marrow growth and differentiation and in antitumor immune surveillance. Studies with transplantable LGL leukemias in F344 rats have demonstrated a great deal of morphological and functional similarity with normal LGL. Similarities were also noted between these LGL tumors and some previously reported cases of human Tγ-CLL. Biochemical analysis of these rat LGL leukemias has resulted in the purification of cytoplasmic granules containing highly cytolytically active material(s). Rabbit antibodies against these granules block both rat and human NK and antibody-dependent cellular cytotoxicity (ADCC). The present studies demonstrate that a granule component(s) is necessary for the lytic activity of LGL in both NK and ADCC, and provide the first direct evidence that a secretory event involving these granules is part of the lytic process.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09246-16 BTB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Characteristics, Regulation and In Vivo Relevance of NK Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	R. B. Herberman	Acting Associate Director	BRMP, NCI
Others:	J. R. Ortaldo	Deputy Head, Natural Immunity Section	BTB, NCI
	L. Mason	Microbiologist	BTB, NCI

COOPERATING UNITS *(if any)*
University of Perugia, Italy (C. Riccardi); University of Rome, Italy (A. Santoni); Victor Babes Institute, Bucharest, Romania (A. Sulica); Preclinical Screening Laboratory, Program Resources, Inc. (J. Talmadge)

LAB/BRANCH
Biological Therapeutics Branch

SECTION
Natural Immunity Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, MD 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.5	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Mouse natural killer (NK) and natural cytotoxic (NC) cells have been shown to be closely associated with large granular lymphocytes (LGL), as has been found previously for man and rats. Procedures have been developed for highly purifying these natural effector cells, by centrifugation on Percoll density gradients and by elimination of contaminating T cells by treatment with monoclonal antibodies to Lyt 1 and 2 plus complement. Fluorescence flow cytometry studies have indicated that the mouse LGL express low amounts of Lyt 1 and no detectable Lyt 2. LGL have also been shown to account for the natural cytotoxic activity of human leukocytes against freshly harvested human tumors and it has been possible to augment such reactivity by culturing these LGL in the presence of interleukin-2. Detailed studies have been performed on the regulation of the development and reactivity of mouse NK cells. It has been shown that various biological response modifiers, including interferon, cause an in vivo increase in LGL in the spleen, along with a change in their physical characteristics. The characteristics of suppressor cells for mouse NK activity have been studied in detail and the relationship between these cells and the effector cells has been clarified. Mouse model systems for induction of hyporesponsiveness to augmentation of NK activity, after multiple inoculations of interferon, have been developed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09247-04 BTB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Natural Cell-Mediated Immunity in Man: Studies of Fresh LGL

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. R. Ortaldo	Deputy Head, Natural Immunity Section	BTB, NCI
Others:	R. B. Herberman	Acting Associate Director	BRMP, NCI
	I. Blanca	Guest Researcher	BTB, NCI
	A. Procopio	Visiting Fellow	BTB, NCI
	A. Gronberg	Visiting Fellow	BTB, NCI

COOPERATING UNITS *(if any)*
NCI-FCRF (G. Scala); MET, NCI (T. Waldmann); IB, DCBD, NCI (P. Henkart); NIH-NCI, Bureau of Biologics (J. Djeu); PO, NCI-FCRF (H. Rabin)

LAB/BRANCH
Biological Therapeutics Branch

SECTION
Natural Immunity Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, Maryland 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.5	1.0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Human natural killer (NK) cells and K cells mediating antibody-dependent cellular cytotoxicity have been shown to be large granular lymphocytes (LGL). The majority of LGL form lytic conjugates with a wide variety of NK-susceptible target cells. The target cell structures involved in NK recognition is being studied and purified. This structure, isolated and partially purified from K562, has been shown to be a glycoprotein of 30-150,000 M.W. Maximal activity in a binding inhibition assay was seen when target structures were associated with lipids. NK cytotoxic factors (NKCF) are being examined for specificity and their mechanism of action. Three distinct steps have been defined for NKCFs; a) production, b) binding to targets, and c) subsequent target lysis. With procedures able to independently measure these events, a variety of agents which have been reported to inhibit NK cell-mediated killing are being tested to determine their site of action. These NKCFs are produced by LGL and have a general specificity pattern similar to intact killer cells. Fresh LGL subpopulations, cultures, and clones of LGL are being tested for reactivity against a variety of NK targets, to identify subsets that demonstrate funtional selectivity. In addition, LGL have been shown to produce IFN-α and β in response to target cells or lectin. Additional lymphokines (interleukin 1 and 2, B-cell growth factor) and the LGL subset producing them, are being examined.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09255-02 BTB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Role of NK Cells and Macrophages in the Control of Metastatic Spread and Growth

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E. Gorelik	Expert	BTB, NCI
Others:	R.B. Herberman	Acting Associate Director	BRMP, NCI
	W. Bere	Biol. Lab. Tech.	BTB, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Biological Therapeutics Branch

SECTION
Natural Immunity Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, MD 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.3	1.5	0.8

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The involvement of NK cells in the antimetastatic effect of the anticoagulant drugs was investigated. The antiplatelet drug prostacyclin (PGI_2) and the anticoagulant agents, heparin and warfarin, were efficient in the inhibition of the experimental pulmonary metastases. This antimetastatic effect was observed only in the presence of active NK cells. When NK reactivity of mice was depressed by pretreatment of mice with antiasialo GM1 serum or cyclophosphomide (Cy), the antimetastatic effect of the anticoagulant drugs was abrogated. Conversely, stimulation of NK cell activity of mice by Poly I:C augmented the antimetastatic effect of the anticoagulant drugs. These data indicate that NK cell activity is crucial for the antimetastatic effects of anticoagulant drugs. Platelet aggregation and fibrin coagulation on the tumor cell membrane surface may be one of the mechanisms responsible for the protection of tumor cells from destruction by NK or other cytotoxic cells. Anticoagulant drugs make tumor cells more vulnerable to the cytotoxic action of blood cells. Adoptively transferred tumoricidal and nontumoricidal peritoneal Mø elicited by Brewer's thioglycollate medium (TGMø) augmented metastases formation in the lungs. These TGMø were also able to abrogate antimetastatic effect of Poly I:C treatment. It was in contrast to the peritoneal Mø elicted by the other tested stimulating media. TGMø inoculated i.v. induced intravascular aggregation of the blood leukocytes and severe changes in the vasculature of the lungs which might help tumor cells to extravasate and develop mestastases. These data could explain the failure of attempts of adoptive immunotherapy with tumoricidal TGMø.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09256-02 BTB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Natural Cell-Mediated Immunity in Man: In Vitro Activated and Cultured LGL

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. R. Ortaldo	Deputy Head, Natural Immunity Section	BTB, NCI
Others:	P. Allavena	Visiting Fellow	BTB, NCI
	A. Procopio	Visiting Fellow	BTB, NCI
	S. Yamada	Guest Researcher	BTB, NCI

COOPERATING UNITS *(if any)*
NIH-NCI, Bureau of Biologics (J. Djeu); Roche Inst. of Molecular Biology, Nutley, NJ (S. Peska)

LAB/BRANCH
Biological Therapeutics Branch

SECTION
Natural Immunity Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, Maryland 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	2.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Human natural killer (NK) cells and K cells mediating antibody-dependent cellular cytotoxicity have been shown to be large granular lymphocytes (LGL). The majority of LGL form lytic conjugates with a wide variety of NK-susceptible target cells. Interferon caused augmentation of NK and K cell activities of LGL and only LGL demonstrated either spontaneous or interferon-activated NK activity. Natural, recombinant and hybrid recombinant alpha, beta, and gamma interferon molecules have been shown to augment NK activity but vary widely in their potency relative to antiviral activity. A recombinant J species of IFN-α has recently been shown to be unable to augment NK at a dose of 10,000 antiviral units; however, it was capable of augmentation of other leukocyte activities and demonstrated antiproliferative and antiviral activities similar to other IFN-α's. This finding has led to studies regarding the structure-function relationship of IFN and NK boosting. IL-2, (T-cell growth factor), in addition to IFN, has demonstrated a potent ability to augment NK activity. This IL-2 mediated augmentation appears to be dependent on production of IFN-γ by LGL, since abrogation of antiviral activity with anti-IFN-γ serum abolishes NK boosting. Fresh ln an attempt to examine this apparent heterogeneity, cultures and clones of highly purified LGL, grown in the presence of IL-2 have demonstrated morphology and cytotoxic patterns similar to fresh LGL. In addition to NK activity, cultured and clones of LGL have been shown to produce a variety of lymphokines (IL-1, IFN, CSF, BCGF).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09257-02 BTB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Functional Activity of Large Granular Lymphocytes in Rats

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. W. Reynolds	Senior Staff Fellow	BTB, NCI
Others:	R. B. Herberman	Acting Associate Director	BRMP, NCI
	T. Barlozzari	Visiting Fellow	BTB, NCI

COOPERATING UNITS *(if any)*
Chugai Pharmaceutical, Tokyo Japan (H. Fukui); Stanford University, Palo Alto, CA (Dr. Eugene Butcher).

LAB/BRANCH
Biological Therapeutics Branch

SECTION
Natural Immunity Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, Maryland 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	0.5	2.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The present studies in rats have demonstrated an important in vivo antitumor role for large granular lymphocytes (LGL), the population of cells known to mediate natural killer (NK) and antibody-dependent cell mediated cytotoxicity (ADCC). The adoptive transfer of LGL into recipients with depressed NK/ADCC activity was shown to restore in vitro tumor cell cytotoxicity, in vivo clearance of tumor cells from the lungs, and to inhibit the development of artifically induced lung metastases. These results provide the first direct evidence for an important in vivo antitumor role for LGL and suggest that the adoptive transfer of highly enriched LGL populations should be further considered as one potential immunotherapeutic regimen in cancer patients. In addition, we have also shown a number of differences in the organ, age and strain distribution between the NK and ADCC effector cells (K cells) populations. Additional experiments are now in progress to utilize these differences between NK and K cells to further investigate the in vivo relevance of these two natural immune systems.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09259-02 BTB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Characterization and Differentiation of NK Cells and Lymphocyte Subsets

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	B.J. Mathieson	Senior Staff Fellow	BTB,	NCI
Others:	J.R. Ortaldo	Deputy Head, Natural Immunity Section	BTB,	NCI
	L. Mason	Microbiologist	BTB,	NCI
	R.H. Wiltrout	Senior Staff Fellow	LMI,	NCI
	R.B. Herberman	Acting Associate Director	BRMP,	NCI
	Y. Yoda	Guest Researcher	BTB,	NCI

COOPERATING UNITS *(if any)*
Laboratory of Microbial Immunity, NIAID (B.J. Fowlkes); Memorial Sloan-Kettering Cancer Center, New York (F.W. Shen); Program Resources, Inc. (R. Overton).

LAB/BRANCH
Biological Therapeutics Branch

SECTION
Natural Immunity Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, MD 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.5	0.5

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The phenotypic characterization of naturally occurring murine cytotoxic cells has been further developed to understand the origin, differentiation and normal function of this population. Cells from spleen, thymus, blood, bone marrow and liver have been characterized. Effector cell activity has been monitored against appropriate targets for both natural killer (NK) activity and natural cytotoxic (NC) activity. Phenotype has been determined by complement (C)-mediated, antibody-dependent cytotoxicity, by flow cytometry analysis (FCA) of immunofluorescence (IF) and by visual morphological assessment using Staphylococcus aureus (SpA) protein A dependent binding. Splenic and bone marrow subpopulations enriched for large granular lymphocytes (LGL) from nylon wool nonadherent cells subjected to density separation techniques have been characterized with a series of monoclonal antibodies (MoAb) to T-cell differentiation antigens, to myelomonocytic antigens and to other hematopoietic subsets. These studies have indicated a consistent failure to obtain a high level of enrichment and purity of LGL from spleen or bone marrow populations of untreated animals. This led us to examine cells from animals whose NK activity has been augmented by biological response modifiers (BRM). In addition, of LGL obtained from livers of BRM-treated mice have been compared to splenic subpopulations enriched for LGL. A pronounced heterogeneity in phenotype between the different populations has been observed. The phenotypic differences may be related to either the BRM used for NK augmentation or to the organ used as a source of cells. Characterization of bone marrow progenitors of NK activity has been initiated to determine whether the precursors share any of the markers found on mature, functional NK cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09275-01 BTB

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 charecters or less. Title must fit on one line between the borders.)*
Effect of Mutagen Treatment on the Immunogenic Properties of Tumor Cells.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E. Gorelik	Expert	BTB, NCI
Others:	R.B. Herberman	Acting Associate Director	BRMP, NCI
	S. Peppoloni	Visiting Fellow	BTB, NCI
	W. Bere	Biological Lab. Tech.	BTB, NCI

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Biological Therapeutics Branch

SECTION
Natural Immunity Section

INSTITUTE AND LOCATION
NCI, NIH, Frederick, Maryland 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.1	1.3	0.8

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The effect of mutagen treatment on the immunogenic and metastatic properties of tumor cells was investigated. After two courses of in vitro treatment of 3LL tumor cells with UV light (254 nm) or B16BL6 melanoma cells with MNNG, highly immunogenic cell variants were obtained. These immunogenic variants of 3LL or BL6 tumor cells were rejected in the immunocompetent C57BL/6 mice, in all irradiated (550R) or athymic nude mice. All 15 clones selected from the parental tumors were able to grow in the immunocompetent mice. Some clones from the mutagen-treated tumor cells (12 out of 80 clones of 3LL and 34 of 48 clones of BL672 tumor) were rejected in 60-100% of inoculated immunocompetent mice, but grew in nude mice (tum^- clones). Mice which were able to reject the first tumor inoculum were resistant to subsequent challenge with high doses of tumor cells. Immunogenic variants of 3LL tumor showed complete cross protection when immune mice were challenged with nonidentical tum^- clones, as well as tum^+ clones or the parental 3LL tumor cells. Mutagen treatment of 3LL and BL6 tumor cells not only increased their immunogenicity but also reduced their metastatic ability.

Using monoclonal antibodies and flow cytometry analyses, the expression of H-2 antigens on the cell surface of the immunogenic and nonimmunogenic tumor cell variants was investigated. A substantial increase in the expression of $H\text{-}2K^b$ and $H\text{-}2D^b$ antigen in the BL6T2 cells and its clone was found. Tum^- clones of 3LL cells also had higher level of H-2 expression than tum^+ cells.

These data indicate that treatment with UV light or MNNG can be efficient in the increase the immunogenicity of tumor cells. The crossreactivity of the immunogenic variants with the parental tumors can be utilized for immunotherapy of the local or metastatic tumors in experimental animals.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 06146-07 BTB

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cellular Regulation by Immune Modifiers and Chemotherapy in the Tumor-Bearing Host

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M.A. Chirigos	Head, Immunopharmacology Section	BTB, NCI
Others:	T. Saito	Visiting Fellow	BTB, NCI
	R. Ruffman	Guest Worker	BTB, NCI
	R. Welker	Microbiologist	BTB, NCI

COOPERATING UNITS *(if any)*

Lymphokine Section, LMI, NCI (E. Schlick); Immunobiology Section, LMI, NCI (R. Wiltrout, G. Varesio); Natural Immunity Section, BTB, NCI (C. Reynolds); Laboratory of Viral Diseases, NIAID (H. Levy).

LAB/BRANCH

Biological Therapeutics Branch

SECTION

Immunopharmacology Section

INSTITUTE AND LOCATION

NCI, NIH, Frederick, Maryland 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.8	2.0	0.8

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Immunopharmacokinetic studies showed that four of seven biological response modifiers (BRMs) tested had a potent ability to augment natural killer (NK) cell tumor cytotoxicity in vivo, (MVE-2, Poly ICLC, Picibanil and αβ IFN). The same four BRMs also strongly stimulated Mø tumoricidal activity, which remained elevated for over 10 days, in contrast to 7 days for NK cell activity. Multiple treatments with the 4 BRMs did not maintain elevated NK activity but resulted in decreased activity, in contrast to a maintained Møactivity. Such hyporesponsiveness to NK boosting by multiple treatments with BRMs was due to a decrease in large granular lymphocyte (LGLs), which are associated with NK cell activity, indicating a failure to maintain the expansion of LGLs.

Seven BRMs were examined in vitro and in vivo for their capacity to induce the production and secretion of regulatory factors (colony stimulating factor, CSF: Prostaglandin E_1 and E_2, PGE; Interferon, IFN). Poly ICLC, Picibanil, αβ IFN and BM 41.332 stimulated Mø to secrete significant amounts of CSF and PGE. Poly ICLC also stimulated IFN secretion. In vivo, Poly ICLC and MVE-2 treatment resulted in significant elevation in serum of CSF but not of PGE. The increased CSF was found to correlate with increased bone marrow (BM) cells and stem cells (GM-CFU-C) developing from BM cells. Since cytoreductive chemotherapy of tumors also leads to depressed NK cell and BM cellularity, MVE-2 and Poly ICLC were examined for their capacity to restore both cell populations following cyclophosphamide (Cy) treatment. Both BRMs caused an earlier restoration of NK and BM cells.

Studies to establish more effective antitumor treatment modalities showed that combined cytoreductive chemotherapy and BRM (MVE-2 or Poly ICLC) resulted in extended survival periods and a substantial number of long-term survivors. Timing of administering the BRM in relation to the cytoreductive agent was critical with a need to give the BRM within 3-4 days following chemotherapy.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 09213-04 LMI

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Characterization of Transforming Growth Factors in Human Urine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E. S. Kimball	Senior Staff Fellow	LMI, NCI
Others:	M. Y. Kim	Visiting Fellow	LMI, NCI

COOPERATING UNITS *(if any)*

N/A

LAB/BRANCH

Laboratory of Molecular Immunoregulation

SECTION

Biochemistry Section

INSTITUTE AND LOCATION

NCI-FCRF, Frederick, Maryland 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have developed a screening procedure for transforming growth factor activity in the urine. Analysis of acid extracts of urine from normal donors and cancer patients by reverse phase HPLC revealed the presence of five EGF-related growth factors with soft agar colony-promoting activity. Determination of EGF activity and quantitation of levels of EGF activity were accomplished using a solid phase radioreceptor assay developed in this laboratory this past year. Of the EGF-related activities oberved using this assay, two were elevated in cancer patients' urines, one of which correlated with a high molecular weight TGF previously shown by gel filtration to be unique to most cancer patients. Another TGF was found at high levels in normal control urines. Thus, using reverse phase HPLC, we were able to resolve five major species of EGF-related TGF. These are functionally similar, but chemically distinct from TGF isolated from tissue culture tumor cells. Distinct qualitative and quantitative differences are seen in TGF urinary moieties of cancer patients compared to normal controls. Purification methods have been developed to allow isolation of the tumor associated urinary TGF in sufficient quantities to allow complete biochemical characterization and comparison to TGF produced by tumor cell lines in tissue culture. Preliminary N-terminal sequence analyses are presently being conducted on the purified TGF and monoclonal antibodies to purified TGF are being raised as well.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09265-01 LMI

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Interleukin 1 and Cytokine Activities in Human Urine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E. S. Kimball	Senior Staff Fellow	LMI, NCI
Others:	S. F. Pickeral	Biologist	LMI, NCI

COOPERATING UNITS *(if any)*
Program Resources, Inc., NCI-FCRF (J. L. Rossio).

LAB/BRANCH
Laboratory of Molecular Immunoregulation

SECTION
Biochemistry Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, Maryland 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Urine concentrates from normal individuals were shown to contain interleukin 1 (IL 1)-like activity when tested directly on human dermal fibroblasts and on C3H/HeJ mouse thymocytes in the presence of 1 ug/ml phytohemagglutinin. Seventy-five percent of the urine samples tested, however, demonstrated the presence of a specific inhibitor of IL 1 promoted thymocyte proliferation. This inhibitor did not affect IL 2-promoted proliferation of mouse thymocytes or CT-6 cells or IL 1-promoted proliferation of human dermal fibroblasts. After gel filtration of the urine concentrates, even those samples that were inhibitory yielded fractions containing both thymocyte and fibroblast proliferative activity. The approximate m.w. of these activities were 75,000 and 15,000. In addition, two peaks of low m.w. thymocyte proliferative activity were noted at 4,000 and 2,000. The 2,000 pool, but not the 4,000 pool, also contained fibroblast proliferative activity. Purification methods are being developed for isolation of the urinary IL 1, to allow complete biochemical and biological characterization and for development of a screening assay to assess the clinical significance of altered levels of these substances.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 09268-01 LMI

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Role of a Human Serum Immunosuppressive Factor in Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Se-Kyung Oh	Guest Researcher	LMI, NCI
Others:	W. L. Farrar, Jr.	Senior Staff Fellow	LMI, NCI
	H. A. Young	Expert	LMI, NCI

COOPERATING UNITS *(if any)*

Department of Microbiology, Boston University, School of Medicine; Biological Therapeutics Branch, NCI (A. C. Morgan).

LAB/BRANCH

Laboratory of Molecular Immunoregulation

SECTION

Biochemistry Section

INSTITUTE AND LOCATION

NCI-FCRF, Frederick, Maryland 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.25	0.25	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We are interested in pursuing the biochemical identity and properties of non-specific humoral suppressor factor in the sera or body fluids of cancer patients. We have previously shown that the major immunosuppressive factor in malignancy may be antigenically related to the E-receptor of human peripheral blood T lymphocytes. During the past few years, we've been trying to delineate the biochemical relationship between the non-specific humoral suppressor factor and the cellular E-receptor derived from human peripheral blood T lymphocytes.

Radioimmunoassay developed with monoclonal anti-E receptor antibody versus purified serum suppressor factor revealed that there is relatively large quantity of this factor (mg/ml range) in the sera of various patients as well as in normal human serum. Sandwich radioimmunoassay developed with detergent-solubilized, purified human T lymphocyte lysate indicated there is a relatively small quantity of the soluble form of cellular E-receptor in normal human serum (ng/ml range), although the levels of this soluble E-receptor are elevated in the sera of various autoimmune disease or cancer patients. Using ^{125}I-labeled anti-E-receptor antibody, we also have studied the mechanism of induction of new E-receptor synthesis and its shedding into culture supernatants using various biological response modifiers. The T cell mitogen, phytohemagglutinin, and the tumor promoter, phorbol myristic acetate, both stimulate the synthesis and release new E-receptors whereas non-T cell mitogens, lipopolysaccharide or interleukins 1 and 2 failed to do so. IL 1, however, can augment lectin-induced E-receptor induction.

We are in the process of elucidating the amino acid sequence of the purified serum suppressor factor the amino acid sequence of E-receptor deduced from the cloned gene that codes for the E-receptor, for comparison of amino acid sequence homology.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 09251-02 LMI

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies of Hematopoietic and Tumor Cell Growth Factors

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E. A. Schlick	Visiting Associate	LMI, NCI
Others:	F. W. Ruscetti	Expert	LMI, NCI
	E. S. Kimball	Senior Staff Fellow	LMI, NCI
	J. J. Oppenheim	Chief	LMI, NCI

COOPERATING UNITS *(if any)*

Immunopharmacology Section, Biological Therapeutics Branch, NCI; Clinical Section, Biological Therapeutics Branch, NCI.

LAB/BRANCH

Laboratory of Molecular Immunoregulation

SECTION

Lymphokines Section

INSTITUTE AND LOCATION

NCI-FCRF, Frederick, Maryland 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Antineoplastic treatment regimens consisting of chemotherapy often result in a dysfunction of hematopoietic precursor cells of the granulocyte-macrophage (GM-CFU-C) lineage. We were, therefore, interested in testing the ability of selected biological response modifiers (BRMs) to modulate growth and differentiation of GM-CFU-C and nucleated bone marrow cells (BMC) in normal and cyclophosphamide (CY)-pretreated mice. In vivo treatment of normal mice with either MVE-2 or poly ICLC induced an increase in secretion of colony stimulating factor (CSF) by BMC and macrophages, which was followed by an increased proliferation rate of GM-CFU-C and BMC. Both BRMs were also able to ameliorate the bone marrow depressing effects of CY pretreatment and to induce significantly enhanced Mø activities when given about 3 days after CY. The present results thus support the concept that selected BRMs might be of value in reconstituting granulocyte and macrophage functions. We are also in the process of identifying whether immortalized human T cells secrete growth factors essential for long-term growth of human pluripotent hematapoietic stem cells in vitro. Identification of such factors (e.g. multi-CSF) could provide a model for studying physiologic regulation of bone marrow cell growth and differentiation and could also allow to sustain proliferating stem cells in vitro as a source of autologous BMC after treatment with chemotherapy. We are further interested in autocrine regulation of tumor growth. We have preliminary evidence that two murine tumors (a Moloney virus-transformed T lymphoma and a spontaneous lung carcinoma) are secreting factors that stimulate their own growth in a clonogenic assay and in suspension culture. These findings could provide the basis for trying to interfere with the respective tumor growth, e.g. by inhibiting the factor(s) or their production.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09254-02 LMI

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Interrelationship of Neuroendocrine Hormones and Lymphokines

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	W. L. Farrar, Jr.	Senior Staff Fellow	LMI, NCI
Others:	H. B. Stull	Biological Laboratory Technician	LMI, NCI

COOPERATING UNITS *(if any)*
National Institute of Mental Health, NIH (C. Pert).

LAB/BRANCH
Laboratory of Molecular Immunoregulation

SECTION
Lymphokines Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, Maryland 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.75	0.75	1.0

CHECK APPROPRIATE BOX(ES)
- [X] (a) Human subjects
  - [ ] (a1) Minors
  - [ ] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The initiation of interleukin-mediated events requires the activation of phospholipase A_2 to produce arachidonic acid (AA) which is subsequently metabolized by the lipoxygenase pathway. This pathway seems to be required for IL 2-induced elevation of cyclic GMP, stimulation of IFN γ production and the regulation of cellular proliferation. Lipoxygenation of AA is also required for IL 1 to induce IL 2 release. Taken together, these data suggest that products of lipoxygenase metabolism modulate the effects of interleukins, whereas the products of cyclooxygenase pathway (produced predominantly by macrophages) may inhibit the activity of lymphokines as well as their production. Based on this proposed model of the intermediate metabolism required for lymphokine-mediated activities, it is now possible to conceive strategies for the identification of new pharmacological agents for the amplification and inhibition of immune responses.

We have shown an increase in opiate receptors on activated T lymphocytes over the level of β-endorphin binding by resting lymphocytes. Associated with increased receptor appearance is the ability of β-endorphin to modulate (uncouple) T-lymphocyte responses to prostaglandins. The mechanism of β-endorphin activity is mediated through specific opiate receptors and does not directly involve IL 2 receptors or the growth promoting activity of IL 2. Both T-lymphocyte proliferation and NK activity are suppressed by the endogenous production of exogenous addition of PGE_2. Based on our data, it is reasonable to assume that the enhancement of IL 2-mediated lymphocyte growth and function by β-endorphin may be attributed to the ability of β-endorphin to mitigate the inhibitory effects of PGE_2 produced in PBL cultures.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09264-02 LMI

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Regulation of Normal and Neoplastic T-Lymphocyte Proliferation and Function

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	F. W. Ruscetti	Expert	LMI, NCI
Others:	J. A. Mikovits	Chemist	LMI, NCI
	S. F. Pickeral	Biologist	LMI, NCI

COOPERATING UNITS *(if any)*

Litton Bionetics, NCI-FCRF (H. Rabin); Dartmouth Medical School (K. Smith); Upstate Medical Center (B. Poiesz).

LAB/BRANCH

Laboratory of Molecular Immunoregulation

SECTION

Lymphokines Section

INSTITUTE AND LOCATION

NCI-FCRF, Frederick, Maryland 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.75	.75	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The T-cell tropic primate herpesviruses, Herpesvirus saimiri (HVS), and the T-cell tropic RNA tumor viruses, human T-cell leukemia virus (HTLV), have both recently been shown by us and others to transform (immortalize) primate and human T-cell in vitro. Transformed cell lines were developed from the peripheral blood cells of an individual marmoset by HVS, HTLV, and by cocultivation with HVS and HTLV. These cell lines as well as several HVS-transformed owl monkey cells are positive for the E-rosette receptor and reactive with a pan-T-cell monoclonal antibody. In contrast to normal T-cells, they do not require added interleukin-2 (IL 2) for growth. An IL-2 specific cDNA probe which hybridizes to RNA from normal PHA-treated primate lymphocytes failed to hybridize to RNA from either HVS or HTLV-transformed marmoset or owl monkey T-cells. The addition of purified IL 2 to HVS-transformed cells stimulated a 2-to 5-fold increase in cell growth while it had no effect on the growth of HTLV-transformed cells. IL 2 receptors were studied by binding of biosynthetically-labeled (^{3}H)-IL 2 to cells and by immunoflurescence binding of anti-TAC, a monoclonal antibody to the IL 2 receptor, as measured by flow cytometry. Results on IL 2 receptor studies indicated that: 1) IL 2 receptors on both HVS and HTLV transformed cells did not cycle on and off the plasma membrane as in normal T-cell growth and 2) HVS-transformed T-cells had normal levels of IL 2 receptors while the receptor density on HTLV-transformed T-cells was 8- to 10-fold higher. Scatchard analysis was consistent with the presence of one class of high affinity receptors on HVS-transformed cells. The addition of purified natural or recombinant IL 2 increased the level of receptors 2-to 3-fold after 24 hrs on HVS-transformed cells but had no effect on receptor density on normal or HTLV-transformed cells. The transferrin receptor also appeared to be upregulated by IL 2 on HVS-transformed cells but two other surface receptors were not. The T-cells co-infected with HVS and HTLV have the phenotype of HTLV-transformed cells. These results indicate that IL 2 receptor physiology varies among transformed T-cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 09216-04 LMI

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Response of Macrophage-Monocytes to BRM: Mechanisms & Pharmacological Modulation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. Varesio	Visiting Scientist	LMI, NCI
Others:	E. Blasi	Visiting Fellow	LMI, NCI
	E. Bonvini	Visiting Fellow	LMI, NCI
	M. Clayton	Microbiologist	LMI, NCI

COOPERATING UNITS *(if any)*

McGill University, Montreal, Canada (E. Skamene).

LAB/BRANCH

Laboratory of Molecular Immunoregulation

SECTION

Immunobiology Section

INSTITUTE AND LOCATION

NCI-FCRF, Frederick, Maryland 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.75	2.0	.75

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Understanding the intracellular and extracellular regulatory mechanisms controlling the activation of macrophages is necessary to maximize the macrophage-mediated lysis of tumor cells. We have defined patterns of activation that will induce tumoricidal and/or suppressive functions in murine macrophages and we are characterizing the intracellular biochemical events associated with the acquisition of cytolytic activity by macrophages. The finding that tumoricidal macrophages have a depressed rate of synthesis of ribosomal RNA led to the discovery that inhibitors of RNA synthesis synergize with lymphokines in activating macrophages. These results suggest a causal relationship between decrease of RNA synthesis and macrophage activation and point to a role for inhibitors of RNA synthesis augmenting the macrophage-mediated antitumor effects. A similar experimental approach is being used to evaluate the role of protein synthesis and methylation reactions in the process of macrophage activation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09260-02 LMI

PERIOD COVERED
October 1,1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Role of Cytokines in Lymphocyte Activation and Inflammation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. J. Oppenheim	Chief, LMI	LMI, NCI
Others:	G. Scala	Visiting Fellow	LMI, NCI
	K. Matsushima	Visiting Fellow	LMI, NCI
	K. Onozaki	Expert	LMI, NCI

COOPERATING UNITS *(if any)*
Biological Therapeutics Branch, NCI (P. Allavena, J. R. Ortaldo and R. Herberman); Medicine Branch, NCI (R. Fisher); Bureau of Biologics, FDA (J. Djeu); Metabolism Branch, NCI (A.V. Muchmore); Laboratory of Pathophysiology, NCI (W. R. Kidwell).

LAB/BRANCH
Laboratory of Molecular Immunoregulation

SECTION
Immunobiology Section

INSTITUTE AND LOCATION
FCRF-NCI, Frederick, Maryland 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	3.0	0.0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have investigated some of the cell sources, biological activities and biochemical characteristics of interleukin (IL 1). We have established that a subpopulation of $OKM1^+$, DR^+, $B73.1^+$ large granular lymphocytes (LGL) with natural killer (NK) activity when stimulated by endotoxin produce IL 1 and can also act as accessory antigen-presenting cells (APC) that have the capacity to activate T lymphocytes. In contrast another subset of LGL (DR^-, $OKM1^-$) can be stimulated by lectins to produce lymphokines such as IL 2 and interferon. In addition, a number of EBV-transformed human B cell line cells were also demonstrated to produce IL 1 and to have APC capabilities. Several of these B cell lines, in addition, spontaneously produced factors that inhibit effects of IL 1, which we have termed "contra IL 1".

Human IL 1 was purified to homogeneity by a sequence of chromatography techniques. Low doses of purified IL 1 were shown to stimulate murine mammary epithelial cells to secrete collagen type IV, a characteristic constituent of basement membranes. In addition, such IL 1 promoted in vitro tumoricidal effects of human monocytes on melanoma tumor cells. This effect of IL 1 could be blocked by indomethacin and emulated by prostaglandin E_1 and E_2 and dbcAMP. These observations suggest that IL 1 may have autocrine functions and through its effect in inducing or maintaining monocyte tumoricidal capabilities IL 1 may participate in host defenses against tumors.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 09262-02 LMI

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Antitumor Effects of Natural Killer Cells and Macrophages in Mice

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	R. H. Wiltrout	Senior Staff Fellow	LMI, NCI
Others:	J. R. Ortaldo	Biologist	BTB, NCI
	C. W. Reynolds	Staff Fellow	BTB, NCI
	B. J. Mathieson	Staff Fellow	BTB, NCI
	R. B. Herberman	Chief	BTB, NCI
	R. R. Salup	Guest Researcher	LMI, NCI
	P. Urias	Biological Laboratory Technician	LMI, NCI

COOPERATING UNITS *(if any)*

Queen's University, Kingston, Ontario, Canada (R. S. Kerbel).

LAB/BRANCH

Laboratory of Molecular Immunoregulation

SECTION

Immunobiology Section

INSTITUTE AND LOCATION

NCI-FCRF, Frederick, Maryland 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.0	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Natural killer (NK) cells and macrophages (MØ) may inhibit formation of metastases. NK cells can function during the bloodborne phase of metastasis, in both normal or biological response modifier (BRM)-treated mice. We have found that highly lytic NK cells can also be induced in the tissue of both the lungs and liver by the pyran co-polymer, MVE-2, and that these cells are efficient in inhibiting the formation of metastases in lung and liver. This was demonstrated by preferentially depleting blood and spleen NK activity, which is important for the intravascular inhibition of metastasis, through the use of defined doses of the NK-specific anti-asialo GM_1 ($asGM_1$) serum. In this model, MVE-2-augmented NK activity in blood and spleen is deleted, while NK activity in the lungs and liver, along with anti-metastatic effects are retained. High doses of anti-$asGM_1$ ablate lung and liver NK activity, as well as anti-metastatic defenses, indicating that tissue NK activity can play an important role in BRM-induced anti-metastatic responses. Further, we have characterized the cells mediating this tissue resistance to metastasis as large granular lymphocytes (LGL), the cells previously associated with NK activity in rats and humans. We are studying the regulation of these anti-metastatic defenses by naturally produced BRMs, and have found that human recombinant IL 2 (hrIL 2) augments NK activity in the liver and peritoneal cavity, as well as of spleen cells in vitro. Further, low doses of hrIL 2 and mouse recombinant γ IFN (mr γIFN) have an additive effect in boosting NK activity in vivo. We are now studying the anti-tumor therapeutic potential of these lymphokines in several experimental models. BRMs also activate MØ for tumoricidal activity. Therefore, doses of anti-$asGM_1$ which ablate all detectable NK activity, but will be used to test the ability of activated MØ to inhibit metastases, in the absence of NK cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CM 09263-02 LMI

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biochemical Aspects of the Functional Activities of Monocytes and Macrophages

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E. Bonvini	Visiting Fellow	LMI, NCI
Others:	L. Varesio	Visiting Scientist	LMI, NCI
	E. Blasi	Visiting Fellow	LMI, NCI
	M. A. Clayton	Microbiologist	LMI, NCI
	E. S. Kleinerman	Senior Investigator	LMI, NCI

COOPERATING UNITS *(if any)*

Division of Biochemistry and Biophysics, CDB, FDA (T. Hoffman).

LAB/BRANCH

Laboratory of Molecular Immunoregulation

SECTION

Immunobiology Section

INSTITUTE AND LOCATION

NCI-FCRF, Frederick, Maryland 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.25	1.0	0.25

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Monocytes and their tissue counterparts, macrophages, have multiple functions in host defense and may play a role against tumors when activated by specific agents to acquire cytolytic or cytostatic capabilities. We have investigated the metabolic changes associated with the acquisition or the expression of cytotoxicity upon in vitro activation by biological response modifiers (BRMs). Peritoneal macrophages from responsive strains of mice, C57BL/6 or C3H/HeN, treated with interferon γ (IFN γ) or LPS, became cytotoxic against tumor targets and displayed an increased intracellular content of the active methyl donor S-adenosylmethionine (SAM). Similarly treated macrophages from the genetically deficient strain of mice, C3H/HeJ, failed to become cytotoxic and had an unchanged SAM content. Turnover studies indicated that the increased SAM content in activated cells was associated with a decreased rate of utilization together with an unmodified synthetic rate. We concluded that the observed changes in SAM metabolism are closely associated with the induction of cytotoxicity in macrophages, and may reflect specific changes in SAM-mediated reactions, including transmethylations.

In human monocytes we found that treatment with IFN γ or lymphokine preparations containing MAF activity induced a higher ability to secrete superoxide anion (O_2^-), a potent antimicrobial agent. However, we failed to correlate this observation with the expression of cytotoxic activity by monocytes, since only MAF-treated cells acquired cytolytic capacity against adherent tumor targets in a long-term cytotoxicity assay. These results indicate a requirement for other mechanisms in monocyte-mediated cytotoxicity.

These studies contribute to understanding the molecular mechanisms of monocyte and macrophage functions, and may help in the rational development of strategies for modulating cellular activities.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09266-01 LMI

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Analysis of the Immunological Response to an ONC Gene Product

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	H. A. Young	Expert	LMI, NCI
Others:	R. H. Wiltrout	Senior Staff Fellow	LMI, NCI

COOPERATING UNITS *(if any)*
Laboratory of Molecular Oncology, NCI (T. Shih, D. Blair); Laboratory of Viral Pathology, NCI (U. Rapp).

LAB/BRANCH
Laboratory of Molecular Immunoregulation

SECTION
Immunobiology Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, Maryland 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project is designed to determine whether immunization of mice with a recombinant DNA-derived onc gene product can lead to protection against a subsequent challenge with tumor cells expressing this onc gene product. Immunization of BALB/c mice will be performed with a highly purified recombinant DNA-derived Ha-ras onc gene product, p21. Mice will subsequently be challenged with 10^5 Harvey sarcoma virus or Kirsten sarcoma virus transformed BALB/3T3 cells in order to determine if protective immunization has been achieved. Cellular immune responses to the onc gene product will also be investigated. Subsequent studies will utilize other recombinant DNA derived onc gene products (e.g. mos) to determine the immunization potential of these proteins. These experiments will provide an important evaluation of the potential usefulness of onc gene products as immune stimuli of host defenses against cancer.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09267-01 LMI

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Analysis of Gene Expression During Lymphokine-Dependent Growth and Differentiation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	H. A. Young	Expert	LMI, NCI
Others:	J. F. Dray	Biologist	LMI, NCI
	D. E. Mizel	Chemist	LMI, NCI

COOPERATING UNITS *(if any)*
Laboratory of Molecular Immunoregulation, Lymphokines Section (W. L. Farrar, F. W. Ruscetti).

LAB/BRANCH
Laboratory of Molecular Immunoregulation

SECTION
Immunobiology Section

INSTITUTE AND LOCATION
NCI-FCRF, Frederick, Maryland 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	0.5	1.0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The establishment of in vitro T-cell clones dependent upon exogenous IL 2 for proliferation has made possible analysis of molecular events which occur during IL 2 stimulation. This project involves construction of cDNA libraries from poly A^+ RNA isolated from an established IL 2-dependent T-cell line and an IL 2-independent subclone, utilizing the cDNA cloning vector λgt10. Studies will be undertaken to identify cDNA clones which are preferentially expressed in the IL 2-dependent cell line in order to identify: 1) direct cellular responses to a specific lymphokine and 2) genetic elements which mediate the cellular response to a lymphokine. In addition these studies will also attempt to identify cDNA clones which are preferentially being expressed in the IL 2-independent subclone in order to understand the events which promote IL 2 independence.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CM 09269-01 LMI

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Regulation of DR Antigen Expression and Shedding

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	H. Gershon	Guest Researcher	LMI, NCI
Others:	J. J. Oppenheim	Chief	LMI, NCI
	Y. D. Kuang	Guest Researcher	LMI, NCI
	S. K. Durum	Senior Staff Fellow	LMI, NCI

COOPERATING UNITS *(if any)*

Clinical Immunology Services, PRI (A. Maluish); Medicine Branch, DCT, NCI (R. Fisher).

LAB/BRANCH

Laboratory of Molecular Immunoregulation

SECTION

Immunobiology Section

INSTITUTE AND LOCATION

NCI-FCRF, Frederick, Maryland 21701

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.75	.75	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Ia/DR antigen-bearing cells play a decisive role in the presentation of antigen to syngeneic T-cells. Studies in this laboratory have demonstrated that Ia/DR expression by monocytes/macrophages can be induced by the cytokines IFN-γ and IFNα and be suppressed by stimulants of a cAMP-mediated pathway such as PGE_2. The state of monocyte/macrophage Ia/DR expression varies with the developmental, environmental and pathological state of the individual. We have demonstrated a low level of Ia/DR expression on monocytes/macrophages from subjects with reduced immune reactivity, including human newborns, SLE patients with defective lymphokine production, and anergic patients with far advanced Hodgkin's disease. Ia/DR antigens are expressed both on the surface of cells and shed from these cells, apparently on lipid vesicles. We have demonstrated significant Ia/DR shedding from human peripheral blood monocytes, a human monocytic cell line, and several EBV^+ B-cell lines, but not from E-rosette forming T-cells. Exposure of peripheral blood adherent cells to human recombinant IFN-γ enhances the expression of DR antigens and subsequent shedding of this material. The role of shed DR material in in vitro immunological reactions is being evaluated. Preliminary results suggest that vesicular DR can activate allogeneic lymphocytes to produce interleukin 2.

DCT NUMERICAL LIST OF PROJECT NUMBERS (1984)

CM-00650-29 ROB

CM-00684-29 ROB

CM-03024-15 NMOB

CM-03403-19 M

CM-03404-13 M

- CM-03580-15 LMCB

- CM-03581-15 LMCB

- CM-03584-12 PRB

CM-03800-14 SB

CM-03801-14 SB

CM-03811-10 SB

- CM-06108-15 LCHPH

- CM-06117-12 LTCB

CM-06119-15 MB

- CM-06140-08 LMPH

- CM-06142-07 LCHPH

- CM-06148-05 LCHPH

- CM-06146-07 BTB

- CM-06150-03 LMPH

- CM-06152-02 LMCB

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