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DIVISION OF CANCER BIOLOGY AND DIAGNOSIS
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EXTRAMURAL RESEARCH PROGRAM

DIVISION OF CANCER BIOLOGY AND DIAGNOSIS

The Extramural Research Program covers three scientific areas: Tumor Biology, Immunology and Diagnosis. These programs are primarily grant based, now that the conscious trend to convert research contracts to research grants has been accomplished. Only a few contracts remain, primarily concerned with support resources or screening efforts.

The budget this year reached \$127,127,000 of which \$122,090,000 were in grant supported projects and \$5,037,000 in contracts (including DCBD's share for the FCRF contract).

The Tumor Biology Program supports a broad spectrum of basic biological research in the areas of growth, invasion and differentiation, directed towards elucidating the molecular and cellular factors that distinguish cancer cells from normal cells. It can be expected that this knowledge will lead to improved methods of diagnosis and treatment of cancer patients. Within the Tumor Biology Program, three areas of investigation receive special emphasis. The first is understanding the basic biochemical mechanisms involved in growth control (i.e., to understand how various biological signals initiate and maintain cell division). This information can lead to the development of specific hormonal and drug therapies. The second area is understanding the molecular changes that lead to tumor invasion. Malignant invasive cells can penetrate surrounding tissues, escape normal host immunological defense mechanisms in the bloodstream, and become established at multiple secondary metastatic sites of growth. Theoretically, if the invasive properties of malignant tumors can be controlled and these tumors confined to particular sites, then metastasis, the major killer in cancer patients, will not occur. The third area is developing detailed biological and biochemical information about processes which can induce cancer cell differentiation. If the genetic program of an actively growing cancer could be changed to terminal differentiation, then the malignant tumor would cease to divide and become harmless to the patient.

Dramatic improvements in technology are contributing to the progress and to the success of cancer research. The ability to routinely produce colonies of cells in culture (i.e., hybridomas) that can synthesize unlimited quantities of a single antibody molecule of desired specificity (i.e., monoclonal antibody) has revolutionized the use of antibodies both as diagnostic tools and as agents for improving immunotherapy.

The area with the most significant new activity is oncogene research. Somatic cell hybridization technology and cytogenetic binding techniques have provided powerful tools for mapping genes to specific chromosome. Improved recombinant DNA techniques have enabled the study of mammalian DNA organization at the molecular level. Microtechniques for DNA sequencing are providing a rapid method for comparing different sequences and predicting amino acid primary structures from the genetic code (i.e., the single amino acid change found the T-24 gene product).

The Immunology Program supports a broad spectrum of basic immunologic research directed at understanding the role of the immune system in the development, growth and spread of tumors. Investigations are carried out in: (1) basic immunology, i.e., how it works and what stimuli generate an immune response; (2) tumor immunology, i.e., how it works and what stimuli generate an immune response system which involves the effect of the tumor cell on the immune system as well as how the tumor cell responds to this interaction; and (3) mechanisms of immunologic intervention, i.e., how the immune system responds to intentional external perturbation for the benefit of the tumor-bearing host, for example, the use of bone marrow transplantation; monoclonal antibodies, interferon and thymic hormones.

Studies on the Acquired Immune Deficiency Syndrome (AIDS), including research on related topics of cell-mediated immunity, mechanisms of immunodeficiency and immunosuppression have become a focus of research activity during FY 1983. Much of the current understanding of the immunologic defect in AIDS is based on an understanding of the function and role of various cell types in the normal immune response, and the regulation and control of the immune response. The ability to recognize a derangement in subsets of lymphocytes of AIDS patients stems from basic studies of the functional and phenotypic properties of these lymphocytes.

The development of monoclonal antibodies, particularly monoclonal antibodies to human T cell differentiation antigens, in conjunction with flow cytometry, has enabled detailed investigations of various functional subpopulations of T cells important in the generation of the immune response.

To understand further the nature of the immune defect in AIDS and other immune deficiency states, one must look at the functional reactivity and interactions of the various components of the immune system. The immune system is composed of a network of regulatory circuits and depends on self recognition for cellular communication and for the cooperative events that enable this system to function effectively. The Ia antigens, products of the immune response genes, are an important set of self determinants recognized by the immune system. Ia antigens are expressed predominantly on non-T cells and can stimulate T cells to differentiate into functional and suppressor cells and to produce various factors including interleukin 2 (IL-2, T cells growth factor) which interact with other T cell to generate various effector T cells. Failure of T cells to recognize Ia cell surface determinants could result in disruption of normal T cell differentiation pathways leading to various immunodeficiency states. The autologous mixed lymphocyte reaction (AMLR) is a well described phenomenon in which T cells proliferate upon culture with syngeneic or autologous non-T cells. It has been postulated that the AMLR may represent an in vitro manifestation of an immunoregulatory mechanism by which B lymphocytes function is controlled. A decrease or lack of AMLR has been observed in several disease states which are characterized by reduced suppression cell activation, and thus to the prediction of autoantibodies. The breakdown of autoimmune regulation may be important in the oncogenic process of certain lymphoproliferative and autoimmune diseases. Basic studies such as these may explain the curious observation that decreased cellular immunity is accompanied by elevated levels of immunoglobulin in AIDS patients.

The normal functioning of the immune system involves the control of its differentiation, the interaction of its cellular components and its response to external stimuli. Another focus of research activity in the Immunology Program is the normal functioning of the immune system involves the control of its differentiation, the interaction of its cellular components and its response to external stimuli. Another focus of research activity in the Immunology Program has been the study of the molecular regulation of the immune system, that is, the expression and interaction of a variety of gene products, including immunoglobulins, soluble mediators, cell surface receptors and antigens. A number of laboratories supported by the Immunology Program are identifying, isolating, purifying and characterizing tumor-associated antigens (TAA's). As the structural and functional nature of these molecules is understood it may provide the basis for improved methods of detection and therapy of various human malignancies.

The Diagnosis Program emphasizes research in early detection, diagnosis, tumor localization, and monitoring changes during therapy or progression of disease. Projects in these areas are frequently concerned with improvement of existing techniques as well as the development of new tests and procedures. Many of the projects in the Cancer Diagnosis Research Program have begun in a more basic area such as, tumor biology and tumor immunology.

The major objective of the program is to recognize or detect cancer at the earliest possible stage to allow appropriate therapy to begin. Early detection and early treatment should improve the chances for the control of cancer, decrease mortality from the disease and increase survival and quality of life of those with cancer. Additionally, early detection is providing greater understanding of the natural history of different types of cancer in the early stages of disease. The Diagnosis Research Program consists of projects in five disciplinary categories: Biochemistry, Immunodiagnosis, Cytology, Pathology, and those projects that are clearly Multiple Disciplinary.

TUMOR BIOLOGY PROGRAM

Description and Introduction

The Tumor Biology Program supports a broad spectrum of basic biological research to determine what cellular and molecular factors distinguish cancer cells from normal healthy cells and tissues. The supposition is that knowledge of these properties and processes will help us learn how to manipulate or change the biological signals responsible for the aberrant behavior of cancer cells. Ultimately, this should result in more effective methods for the diagnosis, treatment and management of cancer victims.

Within the Tumor Biology Program, there are three major areas of investigation which conveniently correspond to different theories of how to control the development and progression of neoplastic disease. The first is understanding the basic biochemical mechanisms involved in growth control, whether these involve particular external signals that initiate the process of cell division or cellular molecules more directly responsible for the control of DNA replication and metabolism. This kind of information can lead to the development of specific hormonal and drug therapies. The second is studying changes that occur at the molecular level which lead to cancer cell invasion. The invasive behavior of cancer cells is a prerequisite to malignancy, or the ability of tumors to invade surrounding tissues, escape normal host defense mechanisms and become established at multiple secondary metastatic sites of growth. Theoretically, if the invasive properties of malignant tumors can be controlled and these tumors confined to particular sites, metastasis, the major killer in cancer patients, will not occur. Treatment of tumors confined to a single site is usually more successful. The third is to develop detailed biological and biochemical information about the processes which induce cancer cell differentiation. There is good reason to believe that many kinds of cancers will respond to external stimuli and differentiate. If the genetic program of an actively growing cancer could be changed to one of terminal differentiation, then the malignant tumor could be rendered harmless. Although the above emphasis of the the Tumor Biology Program in the areas of growth, invasion and differentiation is stated in simple terms, they provide a purposeful way of viewing the role of basic biological research to the ultimate goal of curing cancer.

The kinds of information developed in the Tumor Biology Program provide a foundation for and relate directly or indirectly to nearly every other program area within the National Cancer Institute. The importance of basic tumor biology research to the National Cancer Plan is reflected by the large \$60.0 million commitment of the NCI to this program area in FY 1982 (See Table I). Complete listings and summaries of all grants supported by the Tumor Biology Program are included in the attached Appendices.

As in the previous year the molecular genetics of cancer has aroused the greatest attention from both the scientific and public sectors of the community. Progress in this area is occurring at a very rapid pace and truly represents one of the best examples of how sophisticated, powerful technologies are being combined and refined to understand cancer cell behavior. However, important developments have occurred in other research areas as well. The following report selectively emphasizes those areas which appear to demonstrate the greatest progress and/or promise in the Fiscal Year 1983.

Oncogenes and Cancer

In the past three years, powerful new technologies and the convergence of different scientific disciplines have resulted in the rapid acquisition of information about the long-imagined "cancer genes". Terms such as "oncogenes" and "proto-oncogenes" are now commonly used by the biomedical and lay communities. The fascinating and exciting conclusions which can already be drawn from this very limited glimpse of the cancer process will be discussed. However, this is also a propitious moment to briefly review some aspects of the genesis of oncogene research in order to place current research findings in perspective, as well as to discuss some of the problems of interpretation, especially with regard to understanding how transformation of cells in vitro relates to the initiation and progression of neoplastic disease in vivo, and to project where there may be some changes in the pattern of oncogene research in the near future. Clearly, the rapid pace and expanding nature of this area of tumor biology and virology is sure to result in an annual discussion of results for many years to come.

The molecular understanding of cancer began many years ago when considerable dollars and research effort were devoted to testing the hypothesis that cancers are caused by viruses. Although, unhappily, it could not be proven that viruses were a major cause of human cancer, everything that has been learned in a decade of intensive research on animal tumor viruses has contributed importantly and significantly to our current understanding of human neoplastic diseases. Of greatest importance was the discovery of RNA retroviruses which must convert their RNA information to DNA before integrating themselves into the host genome and successfully exploiting the normal cellular mechanisms involved in RNA synthesis for viral replication and subsequent cell transformation. Two classes of retroviruses were discovered: the acute transforming viruses, which produce a single gene product that can cause neoplastic transformations at an alarming speed, and chronic transforming viruses, which act slower by inappropriately activating the expression of normal cellular genes. Most significantly, it has been shown that acute transforming viruses have acquired this property by inserting into the host cell genome and recombining with normal cellular genes now called "proto-oncogenes." These "proto-oncogenes" once placed under the powerful genetic switch-on mechanisms of retroviruses are called "oncogenes." To this date, all oncogenes discovered in acute transforming viruses, now abbreviated as v-onc, have homologous proto-oncogenes DNA counterparts in normal cells, now abbreviated as c-onc. Although retroviruses will continue to remain important tools for studying the organization and biology of animal cells (Jaenish, 1983), the study of various molecular and genetic mechanisms has become a major new area of research in the Tumor Biology Program.

Nearly twenty v-onc's with c-onc counterparts have been discovered, as noted in the table below (provided kindly by Dr. Charles Sherr of the National Cancer Institute). Although this table is divided into three or four speculative classes of onc genes, it stresses some important generalities. There appear to be only a few oncogene families (Weinberg, 1982), so possibly the number of different genes which can produce single gene products capable of transforming cells is limited. Furthermore, it is apparent that v-onc gene protein products within these families are different and probably exert their effects through different biochemical mechanisms. Some v-onc's code for cytoplasmic protein kinases or protein kinase-like products, while others code for plasma membrane protein components, nuclear protein components and possibly growth factors.

*Table - Families of v-onc Genes

	<u>Nomenclature</u>	<u>Origin</u>	<u>DNA Nucleotide Sequence Known</u>
IA	Oncogenes with known protein tyrosine kinase activity-cytoplasmic location.		
	v-src	Rous Sarcoma virus (Chicken)	Yes
	v-fps (fes)	Fujinami Sarcoma virus (Cat)	Yes
	v-yes	Yamaguchi (Y73) Sarcoma virus (Chicken)	Yes
	v-ros	UR2 Sarcoma virus (Chicken)	No
	v-abl	Abelson Murine Leukemia virus	Yes?°
	v-fes	Feline Sarcoma virus	Yes
IB	Oncogenes with Nucleotide sequence homology to IA genes but no know activity in present assays.		
	v-mos	Moloney Sarcoma virus (Mouse)	Yes
	v-rel	Reticuloendotheliosis virus strain T (Mouse)	No
	v-fms	Feline Sarcoma virus (McDonough strain)	Yes?°
	v-raf	Murine transforming virus	Yes?°
	v-erb	Avian erythroblastosis virus (Chicken)	Yes?°
II	Ras gene family: p21 protein with GTP & GDP binding activity - plasma membrane location.		
	v-ras ^H	Harvey Sarcoma virus (rat, mouse)	Yes
	v-ras ^K	Kirsten sarcoma virus (rat, mouse)	Yes
	v-bas	Balb/c sarcoma virus (mouse)	No
	+c-ras ^N	Neuroblastoma (human)	No
III	Oncogenes which encode nuclear proteins.		
	v-myc	Myelocytomatosis virus strain MC29 (Chicken)	Yes
	v-myb	Avian myeloblastosis virus (Chicken)	Yes
	v-ela	Adenovirus	
IV?	Oncogenes which encode for growth factors		
	+c-b-lym	Human Lymphomas	No
Other?			
	v-sis	Simian Sarcoma virus	No

* This table provided by Dr. Sherr is included in this report as a demonstration tool and is not meant to serve any scientific documentation purposes.

+ identified to date only by transfection in NIH/3T3 - no v-onc counterpart yet identified

° believed to be sequenced but not yet published in the scientific literature

With the background noted above, it is useful to recapitulate some of the conclusions reported previously before discussing this year's experimental results and implications. We were aware that cancer cell lines carried pieces of DNA that could, under the proper conditions, transform NIH/3T3 mouse cells in vitro, that these pieces of DNA were homologous to viral transforming genes, that normal cells carried similar DNA sequences, and that these normal cell sequences when attached to viral "switch-on" control elements could also transform NIH/3T3 cells. Within mammals, most oncogenes were tissue specific rather than species specific. The major conclusion reached was that cancer is an aberration of gene regulation leading to the excessive synthesis or expression of normal gene products at the wrong time. However, despite the enthusiasm that was generated within the biomedical community, there were a number of experimental and theoretical reservations about oncogene research. Was the NIH/3T3 transfection assay for c-onc's valid when the ultimate proof would be transformation of the same parent cell type? Were the oncogenes discovered in cancer cell lines artifacts of culture conditions or are these same oncogenes also present in primary cancer tissues? How could the well-established theory of a multistep carcinogenic process be reconciled with a single transforming event? What possible mechanisms might be operating to produce overexpression of a normal gene product? All of these questions have been addressed to some extent and it is possible to arrive at further conclusions.

Although it was possible that oncogenes were an artifact of cell lines which had been cultured in vitro over multiple generations, this idea has been dispelled by the detection transforming genes in three human lymphomas (Lane et al., 1982) and in a variety of human carcinomas (Pulcani et al., 1982). Four patient DNA isolates of human pre B, mature B, intermediate T and mature T lymphocyte neoplasms induced transformation of NIH/3T3 cells with high efficiencies. In addition, unmanipulated human solid tumors, including two carcinomas of the colon, and one each of the lung and pancreas and a rhabdomyosarcoma contained a common oncogene which was capable of inducing malignant transformation of NIH/3T3 mouse cells. Therefore, in vitro manipulation of cancer cells does not contribute any special confusing factors to our current understanding of oncogenes.

The continued use of the NIH/3T3 mouse cell line to score for oncogenes has received considerable criticism (Logan and Cairns, 1982). First, NIH/ 3T3 mouse cells already are immortal in the sense that they will grow indefinitely if provided with enough space and culture medium. It could be argued that they are already part way to becoming a cancer cell, and for that reason may not provide the right assay for certain kinds of tumorigenic DNA. Many scientists have clearly stressed that the 3T3 transfection assay cannot be reconciled with our knowledge of carcinogenesis as a multistep process; the assay only detects genes which produce dominant alterations in cell behavior (Cooper, 1982). Most tumors do not yield DNA that can transform 3T3 cells; thus, the assay is incapable of detecting the genetic events responsible for many types of cancer. This last criticism may be due, however, to the way in which laboratories have selected for the clone of 3T3 cells used in the transfection assay. Only one laboratory has been able to detect oncogenes other than those in the ras family (see table) using a 3T3 assay (Lane et al., 1982). Only one in a million cells acquire and express the oncogenes within the exogenously added DNA, suggesting that even within the 3T3 cell population there are only few cells possessing a special genetic or metabolic alteration that makes them competent for transformation.

Even those who use the NIH/3T3 cells are using different clones from the same stock, so there really has been no effort between the various laboratories to standardize the assay. One area of rather intense experimentation is the development of new transfection systems with normal cells and other cell lines. This would confirm the results obtained with NIH/3T3 mouse cells and possibly result in the detection of whole new families of oncogenes.

The single most important theory that has emerged within the recent past is that the dominant expression of oncogenes leading to neoplastic transformation is the result of excessive synthesis or increased activity of a normal "protooncogene" product. There are a number of ways in which a normal gene, ordinarily under strict control, might be switched on to produce an aberrant or neoplastic cell phenotype. A mutation, possibly produced by a carcinogen, could result in an altered protein product with increased activity or new activity. This would be the most surprising result because mutations usually result in amino acid substitutions that cause drastic structural changes in protein structure and concomitant loss or reduction of any biological activity. A second possibility is the movement of a normal gene to a position on a chromosome where there are strong switch-on signals that increase the gene's expression. Interestingly, the most accepted theory of carcinogenesis states that human cancers are usually the result of transpositions/deletions of genetic material rather than mutations. A corollary to this would be the insertion of a virus containing a strong switch on signal into a chromosomal position which turns on the cellular protooncogene. In each case, the normal gene is controlled by a strong switch-on signal that increases gene transcriptions. A third possibility is that the normal gene has become amplified within the cellular genome and increased expression is due to the greater availability of the gene for transcription. A fourth possibility is that modification of the DNA, such as methylation, results in increased or decreased activity of onc genes. A fifth possibility is that increased amounts of normal gene product are the result of more efficient messenger RNA processing or translation. There is strong evidence that all of the first three possibilities may occur in human cancers. The fourth and fifth possibilities are more difficult to test and will probably require greater knowledge of both DNA modification enzyme and c-onc protein products.

At the beginning of this year a number of laboratories were concentrating their research efforts on the c-H-ras gene from the human bladder carcinoma cell line, T24. This has been an especially important problem because most human tumors are carcinomas and all carcinomas to date appear to contain onc genes belonging to the ras family of genes. As reported in last year's annual report, the ras gene protein product (p21) has been identified and localized to the innerside of the plasma membrane of the transformed cell. The most surprising finding is that the only significant difference between the c-ras of the T24 cancer cell line and the c-ras of normal bladder is a single amino acid change resulting from a single nucleotide base change. This has been confirmed by four different laboratories using restriction enzymes (Taparowsky et al., 1982) and by the nucleotide sequencing of the bladder carcinoma oncogene and its normal homologue (Tabin et al., 1982; Reddy et al., 1982; and Capon et al., 1983). Transformation by the bladder oncogene is not due to increased formation of the ras gene protein product. Instead, the transforming protein is considerably more effective, possibly 100 times more potent, in inducing the transformed phenotype. In this case the most unexpected situation seems to be true; transformation is due to a point mutation which either increases the normal activity of the gene product or provides it

with a new function. While this unusual and exciting result initially stimulated much speculation, a recent systematic study of ten primary bladder carcinomas, nine primary colon carcinomas and ten carcinomas of the lung did not exhibit this mutation (Feinberg et al., 1983c). Thus, although the T24 cell line represents an interesting model system, the general significance of point mutations as a cause of human cancer is still an open question. There is no doubt from experiments reported last year that ras genes can be activated by a second independent mechanism which uses strong "switch-on" signals to increase rates of onc gene expression.

Recently, two other pieces of information have emerged about ras genes. A new gene belonging to the ras family has been identified in three human neuroblastoma cell lines which are weakly homologous to both v-ras^H and v-ras^K and produce increased levels of a protein serologically and structurally related to the p21 protein (Shimzu et al., 1983). In addition, the c-ras gene for bladder carcinoma has been mapped on chromosome 11. As will be discussed later, the relationships between c-onc gene chromosome positions and cancer has produced interesting results with onc genes other than ras. It will be interesting to see if the ras gene maps to chromosome 11 in both carcinomas and neuroblastomas and/or if there is any evidence of transpositions to other chromosome locations.

With the development of higher resolution chromosome banding techniques for cytogenetic analysis, there has been increased speculation that most cancers may exhibit nonrandom chromosome rearrangement defects (Yunis, 1982a; Yunis 1982b). Since this is one way in which c-onc's within the genome could be relocated to regions where there are strong cellular "switch-on" signals, many laboratories have set out to determine the chromosome locations of the various onc genes. C-myc has been located on chromosome 8 (Dalla-Favera et al, 1982a), c-fes and c-abl on chromosomes 15 and 9, respectively (Heistercamp et al., 1982), and c-sis on chromosome 22 (Dalla-Favera et al., 1982b). Two important observations already emerge from initial mapping studies. First, c-onc genes are not clustered on any particular chromosome within the human genome. Second, all of the chromosomes containing c-onc genes so far are involved in specific rearrangements found in certain forms of human cancer.

In several different forms of cancer, the chromosome position of c-onc genes has been correlated with non-random chromosome translocations. For the famous Philadelphia chromosome associated with chronic myelocytic leukemia, part of chromosome 9 carrying the c-abl proto-oncogene is translocated to chromosome 22 (Klein et al., 1982). Many laboratories have devoted considerable attention to translocations of the c-myc oncogene, which has been linked to both human Burkitt's lymphoma and mouse plasmacytomas, tumors of the antibody-producing cells. About two years ago, George Klein of the Karolinska Institut in Sweden hypothesized that rearrangements of immunoglobulin genes might be important to the development of some B-cell lymphomas, specifically that translocations could introduce oncogenes into the transcriptionally active sites of the immunoglobulin constant region gene segments. Three independent groups of scientists subsequently demonstrated that in human Burkitt's lymphoma c-myc is translocated from chromosome 8 to 14 (Dalla-Faver et al., 1982b.; Taub et al., 1982; Neel et al., 1982). In addition, an analogous situation occurs in mouse plasmacytomas where the c-myc proto-oncogen is translocated from chromosome 15 to chromosome 12 (Crews et al., 1982; Shen-Ong et al., 1982; Adams et al., 1983). Since chromosome 14 in the human and chromosome 12 in the mouse each carry the DNA coding for heavy chain segments of immunoglobulin

lins, the c-myc has been translocated to regions of potentially active transcription (i.e. strong switch-on control regions within another chromosome). However, the question of whether this translocation event results in increased expression of the c-myc gene has not been completely resolved. In the mouse plasmacytoma situation, it appears as if there is no increase in the level of RNA transcripts but an altered gene product (Shen-Ong et al., 1982; Adams et al., 1983), while in human Burkitt lymphomas there is transcriptional activation of the c-myc gene (Erikson et al., 1983). However, others argue against any significant increase in c-myc expression in Burkitt's lymphoma (Maguire et al., 1983). It is also interesting to note that in both the HL-60 leukemia cell line and primary leukemia cells from the same patient, the c-myc gene is amplified and increased expression occurs without any structural alterations (Dalla-Favera et al., 1982c). The c-mos gene is rearranged in chemically induced mouse myelomas, another form of lymphoid neoplasm. When the nucleotide sequence of the normal and myeloma c-mos genes are compared, the cancer cell contains an oncogene which has lost 500 nucleotides, including the first 88 amino acids of the c-mos protein (Rechave et al., 1982). The mechanism of activation of c-mos becomes as much a mystery as the point mutation in T-24 c-H-ras. Thus, it would appear that for different kinds of lymphocyte tumors, translocations, leading to altered gene products and/or increased transcription or gene amplification can operate to increase the dosage of an oncogene product. Comparisons of oncogene nucleotide sequences and more knowledge of their protein products is sure to provide clearer mechanistic interpretations in the future.

Two very interesting studies have emerged from Geoffrey Cooper's laboratory, important because none of the oncogenes discovered are related to the transforming genes of acutely transforming retroviruses. The first study is one of the few on record to demonstrate transfection of the NIH/3T3 assay system with genes other than those of the ras family. It was demonstrated that specific transforming genes are activated in B and T lymphocyte neoplasms representative of specific stages of differentiation within these cell lineages (Lane et al., 1982). Interestingly, some of the acute transforming viral oncogene homologues, c-fos, c-abl and c-fms are also associated with stage specific and tissue specific expression, suggesting participation of oncogenes in normal developmental processes (Muller et al., 1982, Adamson; personal communication). A second very interesting observation comes from the cloning and nucleotide sequencing of a transforming gene detected by transfection of chicken B-cell lymphoma DNA (Goukin et al., 1983). This oncogene is homologous to a small family of normal cell genes which are highly conserved throughout vertebrate evolution, but possibly more startling is that this gene encodes a small protein which shares striking sequence homology with proteins of the transferrin family. Years of research trying to define the minimum requirements for cell growth have found that transferrin is absolutely required by all mammalian cells cultured in vitro.

Although direct transformation by onc genes homologous to those present in acute transforming retroviruses has received the most attention, there are examples of transformation by chronic retroviruses which operate by indirect mechanisms over long periods of time. Progress is just starting in this area but chronic retroviruses may be better suited to study the progressive alterations which appear to occur during carcinogenesis. Transfection of NIH/3T3 cells may be identifying a small subset of dominant cellular transforming genes which are involved only in the final step of oncogenic transformations (Cooper, 1982).

Two factors are likely to change the emphasis of oncogene research in the future. The first is obvious and has been stated already - that new transfection systems must be developed which will be useful in studying stage-specific oncogenes and multiple event transformations. Many laboratories are working on this problem. The second, and possibly most important, is that without intensive research on the actual oncogene products we will never discern the actual biochemical mechanisms involved in neoplastic-transformation. The rapid pace of oncogene research has provided many important correlations, speculations and contradictions which must be resolved, but few insights into the activities and sites of action of oncogene protein products. Nevertheless, some significant advances in our understanding of the mechanism of transformation have occurred with class IA oncogenes (see table), which exhibit protein kinase activity. As reported in the past, oncogenes that produce protein kinases exclusively phosphorylate tyrosines residues, which up until three years ago had never been observed. Now, we know that tyrosines are phosphorylated in normal cells but that the number of phosphorylated residues increases 5 to 10 fold in transformed cells. We also know that the growth factors, EGF and PDGF, bind to receptors which phosphorylate tyrosine residues. Growth receptor phosphorylation is a transient phenomenon dependent upon the presence of the factor while oncogene protein kinase activity is turned on all the time, as one might expect for a cell which has lost growth control. Most researchers would like to demonstrate a link between oncogene tyrosine kinases and growth hormone receptors, but no success has been reported. Recently, however, it has been discovered that three glycolytic enzymes are phosphorylated in transformed cells (Cooper et al., 1983). Although the significance of this observation is unknown, in most transformed cells glycolysis is perturbed. The fact that there are five to six separate cellular oncogenes with tyrosine kinase activity (see table), which are conserved throughout the animal kingdom, strongly suggests that this kind of phosphorylation is important to normal cell function. Another recent observation has shown sequence homology between the p21 ras gene product of bladder carcinoma cells and mitochondrial ATP-synthase (Gay and Walker, 1983). Possibly, p21 may form part of an enzyme that uses purine nucleotides in catalysis or be involved in cell energy metabolism.

There are many reasons to be cautious as well as excited about drawing general conclusions from oncogene research. One major problem with many of the studies of oncogenes has been the concentration on neoplasms of the blood system, which typically exhibit translocations of chromosomes. Unfortunately, tumors of solid tissues, which are far more common, appear to involve deletions rather than translocations (Marx, 1982). The most exciting general observation, however, is that the oncogenes are conserved throughout phylogeny and are expressed at different times during normal growth and development. Although we must pursue the possibility that identification of cellular oncogenes may eventually allow us to enumerate and recognize the several steps in tumorigenesis, we may also solve many of the riddles of normal growth and development along the way (Bishop, 1983).

Methylation and Gene Regulation

Over the past few years, numerous reports have appeared suggesting that methylation of tRNA and RNA may be involved in the regulation of protein synthesis. These include observations that exposure of test animals to carcinogens elevates the level of tRNA methyltransferases and results in the excretion of methylated

nucleosides, and, that certain antiviral agents inhibit methylation of viral mRNA (Borek, 1982; Goswami et al., 1982).

More recently attention has turned to the concentration of methyl groups on DNA, comparing different tissues, temporal changes in tissues as they undergo differentiation and in normal cells compared with comparable tumor cells. Methylation is becoming recognized as a potential mechanism for switching genes off and the correlation between hypomethylation and increased gene activity is becoming stronger. The actual methylation process is apparently a function of a maintenance methyltransferase that acts on vertebrate DNA after replication, efficiently modifying only cytosine residues to 5-methylcytosine (m^5C) as directed by some biological program. Growth of cultured cells in media containing 5-Azacytidine (azaC) which presumably substitutes for cytosine residues in DNA, has become an important tool in testing the physiological importance of methylation. AzaC cannot be methylated by the cellular enzymes. Growth in azaC of proliferating chick cells carrying an inactive retrovirus loci results in hypomethylation of the DNA and induces transcriptional activity of the viral gene (Groudine et al., 1981). The re-activation of an inactive X-chromosome has also been demonstrated with this technique (Jones et al., 1982). Virally transformed mouse cells containing an inactive thymidine kinase (TK) gene reexpressed TK after azaC treatment. Further study of the methylation patterns of the DNA from cells with either an active TK gene (TK^+) or inactive gene (TK^-) showed the active gene to be unmethylated, the inactive gene methylated (Clough et al., 1982).

Compared to most other types of mammalian DNA examined, brain and thymus (relatively inactive transcriptional tissue) DNAs were hypermethylated, and the "highly repeated" DNA sequence fraction was more methylated than the "moderately repetitive" or "single copy" fractions (Gama-Sosa et al., 1983a). In a more specific analysis, the distribution of the m^5C among dissimilar classes of DNA fractions was compared in nuclei from human brain and placenta (a tissue high in transcriptional activity). Although unfractionated DNA, single gene copies and the Eco repeat family all have higher levels of m^5C in brain than placenta, the Alu family of highly repeated DNA sequences, which is 5% of the genome, showed very little variation in methylation levels between the two types of cells, suggesting that some kind of selective modification within the genome is occurring (Gama-Sosa et al., 1983b). Further evidence of selectivity is apparent from a comparative study of the DNA from benign neoplasms, primary tumors and metastatic neoplasms which revealed a decrease in the m^5C content with increasing tumor progression.

Additional evidence of a potential link between hypomethylation and malignancy was reported in a study of both primary tumor tissue and adjacent analogous normal tissue from patients who had not received any kind of therapy. The restriction endonucleases utilized in this study cleave CCGG sequences throughout DNA but are not active when the cytosine is methylated. The number of fragments generated thus identifies the methylation state of the DNA, the fewer methyl groups the greater the variety of fragment sizes, allowing the detection of more copies of specific genes or DNA sequences. The number of different copies of the specific genes human growth hormone, gamma globin and alpha globin, which represent widely scattered chromosomal locations in the genome, was then assessed with specific cDNA probes. These genes should not normally be expressed in the type of colon and lung tumors examined in this study, yet the results showed that, when compared to the normal tissue of the same patient, there was a substantial hypomethylation in these three specific genomic regions of the human cancers (Feinberg and Vogelstein, 1983b). When the methylation status of the cellular oncogenes c-Ha-ras and

c-Ki-ras were examined in a similar study of normal tissue and primary colon or lung carcinoma tissue from a group of patients, the c-Ha-ras gene in the tumors was found to have a higher degree of hypomethylation whereas the c-Ki-ras was not so profoundly different between normal and carcinoma tissues (Feinberg and Vogelstein, 1983c).

Recently, the total genomic DNA methylation was analyzed in 20 cell lines from different types of human tumors and compared with cultured normal human diploid fibroblasts. The majority of tumor cell lines had decreased levels of methylated DNA, ranging as low as 1.2% of cytosines methylated compared to a value of 3% or more for normal cells (Diala et al., 1983). The methylation patterns of three specific cellular onc genes in a variety of cultured human tumor cell lines were also assessed in comparison to normal fibroblasts. The interesting differences found showed both a gene specificity and a cell line specificity. For c-sis and c-myc there was no particular "tumor" pattern in degree of methylation but the patterns were specific for a given cell line for each of these two genes. In contrast, the c-Ki-ras gene was more highly methylated in all cell lines examined. The suggestion is that specific methylation of cellular onc genes may be important in their function and perhaps in transformation itself (Cheah and Hoffman, unpublished data).

Evidence is also mounting that carcinogens may function, in part, by a mechanism involving methylation. During DNA synthesis, each freshly replicated new (unmethylated) DNA strand is scanned for potential modification sites by a maintenance methyltransferase. The new strand is then methylated at the same cytosines as is the old DNA strand. Using a hemimethylated DNA as substrate, a wide range of chemical carcinogens were tested for their ability to inhibit methylation by this methyltransferase. In some cases the carcinogens altered the DNA so that the enzyme no longer recognized it, in others the carcinogen inactivated the enzyme itself. These agents may therefore cause heritable changes in ^{m5C} patterns leading to alteration of gene expression, perhaps even causing activation of transforming genes themselves (Wilson and Jones, 1983).

Intermediate Filaments

The cytoskeleton of a eukaryotic cell encompasses those cellular entities that are insoluble after neutral detergent extraction. The most insoluble of skeletal structures are the intermediate filaments (IF's), proteins of 100Å diameter, whose function is unknown, and upon which recent speculation has centered. At least five types of IF's have been described: cytokeratins (filaments made of keratin-like proteins) found in epithelial cells; vimentin filaments of mesenchymal cells; desmin filaments of muscle cells; neurofilaments of neuronal cells; and glial filaments found in astroglia (Lane and Anderton, 1982; Osborn and Weber, 1982). These cells can be subdivided according to type of IF, which in turn can offer information about the origin or classification of a tumor. In instances where a patient has metastatic cancer and the primary tumor is unknown, the type of IF found in the tumor cells may help localize the site of the primary tumor, due to the similarity of cytokeratin pattern between tumor cell and tissue of origin (Moll et al., 1982). In addition, in situations where tumor diagnosis can not be made by normal histologic procedures and treatment depends upon the accuracy of the diagnosis, the type of IF in the tumor cell can offer useful clues. Caution must be observed for in vitro applications, however, because tissue culture can modify IF expression. F.C.S. Raemekers reports that, while

solid epithelial tumors contain keratin IF's exclusively, the same cells present in ascites or pleural fluid express vimentin, as do most cultured cells. This phenomenon may give insight into the possible role of vimentin in tumor metastasis and spreading because it appears to be an adaptation to in vitro culture conditions (Ramaekers et al., 1983). In addition, another group has demonstrated differing keratin patterns in epidermal and mesothelial cells, and noted the synthesis in many carcinoma lines of keratins different from their originating cell type. They suggest that the keratin subunit type is important for performance of differentiated function by the cell and perhaps different keratins confer variations in physical and chemical capabilities of the IF's -- such as flexibility, association with neighboring filaments, and, ultimately, cell shape and histological organization (Wu et al., 1982).

As the molecular nature of IF's is elucidated, an understanding of their function can be expected to follow. A number of studies are approaching this problem. The presence of three types of dimers has been demonstrated in cultured baby hamster kidney cells: vimentin-vimentin, vimentin-desmin, and desmin-desmin. These proteins can be integrated into the same IF or found in IF's of close proximity, oriented with cysteine residues in mirror-image symmetry (Quinlan and Franke, 1982).

Neurofilaments have been solubilized and reconstituted in vitro. These IF's contained 200-, 150- and 68-kilodalton triplet components as well as small amounts of other polypeptides. The 68-kilodalton triplet can be purified and reassembled into filaments of approximately 100Å diameter suggesting that this polypeptide is an integral IF wall protein and should be considered as an IF subunit (Zackroff et al., 1982).

A wide body of information has been generated for the cytokeratins. Most of the other IF's are made of one subunit protein, but cytokeratin filaments are members of a complex family of many different peptides. A given epithelial cell can be characterized by its specific pattern of cytokeratin peptides (Moll et al., 1982), although this characterization of epithelial tissue is complicated by its cellular heterogeneity. Interestingly, the vast majority of cancers are carcinomas, of epithelial origin, so an understanding of the cytokeratins could have very direct relevance to cancer research. S. Tseng and coworkers have studied the tissue distribution of epidermal keratins using monoclonal antibodies and discovered that the type of keratin expressed was correlated with differences in epithelial differentiation (Tseng et al., 1982). They distinguished seven keratin classes which may provide useful in vivo and in vitro markers of various epithelial cell types. Only two classes of keratin are expressed in suprabasally located, terminally differentiating epidermal cells. Involucrin is a keratinocyte protein incorporated into the crosslinked envelope during terminal differentiation and normally seen in those cells in a non-basal position. F. Watt and H. Green determined that synthesis of involucrin does not depend on where a cell is located. In fact, the suprabasal cell position is a consequence, as opposed to a cause, of terminal differentiation, since it appears that as cells differentiate and enlarge, they move out from the basal position, perhaps as a consequence of decreased adhesiveness (Watt and Green, 1982).

I. Hanukoglu has provided the first amino acid sequence for a cytoskeletal keratin, and has noted partial homology with other IF proteins, suggesting a distant evolutionary relationship. While major sequence divergence is also ap-

parent, IF's appear to retain sequences compatible with the secondary structural features apparently common to all IF's. Possibly these sequence changes enable the various IF's to meet the cytoskeletal requirements of the particular cell type in which they reside (Hanukoglu and Fuchs, 1982).

Studies on a neurofilament protein NF68, a muscle-specific desmin, and a mesenchymally-derived vimentin, all within the 52-68 kilodalton range, have shown regional sequence homology of between 41% and 72% in non-helical areas of the proteins, supporting the hypothesis that many IF's belong to a multi-gene family and are expressed in conformance with certain rules of embryonic differentiation (Geisler et al., 1982). This group notes similar distributions of tryptophan and cysteine residues in desmin and vimentin.

A group looking at keratin and vimentin in bovine kidney epithelial cells and human Hela cells has demonstrated an unusual phenomenon: IF bundles progressively unravel during mitosis, aggregate into spheroid bodies, and gradually reestablish their filament bundles in telophase. Similar structures have been observed in some solid human carcinomas. Studies are underway to determine the cellular factors promoting this reorganization of IF's into alternate structures (Franke et al., 1982). Utilizing monoclonal antibodies that cross-react with a component of vimentin, R. Dulbecco and associates discovered that this IF is equally present in both sparse and dense cultures but it is rearranged in such a way that the marker epitope apparently increases in accessibility as cell density decreases. This epitope also becomes exposed as the filaments elongate and this rearrangement may provide a framework for cellular motility (Dulbecco et al., 1983).

In summary, both the similarities and differences among the various IF classes are intriguing. The studies described should form the basis for an understanding of the functional nature of these proteins. Meanwhile, the potential diagnostic applications of intermediate filaments can be expected to attract expanded attention.

Models of Metastasis

From the clinical perspective, it is not so much the growth of a tumor that is responsible for the morbidity and mortality of cancer, but other neoplastic properties, especially the capacity for invasion and metastasis. However, progress in understanding these properties has been somewhat slow. It is apparent that the spread of cancer depends on a series of events that take place at the surface of the tumor cell and in the vascular system of the host (Folkman, 1982); however, these events are not understood at a molecular and cellular level because experimental systems designed to examine mechanistically these in vivo processes are few in number. Primary tumor invasion probably involves physical pressure of the growing tumor, adhesiveness and migratory activity of the tumor cells, endogenous hydrolytic activity, chemotactic factors and host response to the tumor. In addition, metastasis involves entry into the circulatory system, survival in the blood stream, exit from the vessels and small capillaries, and invasion and establishment of growth in secondary tissues.

Once the primary growth of a malignant tumor has been established, the metastatic process may begin. The first phase is the entry of malignant cells into the circulation by passage through the walls of the vessels of the tumor. Studies

with rat myelogenous leukemia cells and the mouse B16 melanoma demonstrate that migration occurs through an intact vessel endothelium by selective entry through a temporary migration pane in the endothelial cell body, i.e. transcellular passage without any local destruction (De Bruyn, 1980). Apparently a very great number of cells escape from the tumor, into the circulation, but only about 1% avoid being destroyed by blood factors. For a variety of causes the overall efficiency of the whole metastatic process is low (Weiss, 1982)

The metastatic cell itself may develop specific characteristics that prolong its survival, by passing through several stages of increasing malignancy so that the progeny often exhibit more highly malignant features than the parent. There is also evidence that neoplastic cells acquire genetic instability and that a clone of such cells can expand into variant populations, some of which have a selective advantage in the host. A predominant subpopulation develops that expresses the malignant phenotype, loss of differentiated characteristics and invasion and metastasis (Folkman, 1982).

Perhaps the tumor cell system used most widely for studies of metastasis is the mouse melanoma system, called the B16, developed by Fidler (Fidler, 1973). Specific B16 clones were isolated by administering the melanoma cells intravenously into mice, harvesting the lung metastases and re-administering those cells into new host mice. The resulting cloned lines represent cells that metastasize with high frequency to the lungs but no other organs, and to cells that metastasize very poorly, to any organ. Subsequently lines that colonize selectively in the brain, the liver and the ovary have also been established. This interesting observation suggests that properties on the surface of a cell can determine its fate and its site of metastasis, because the endothelium of one organ can be differentiated from that of another. It further suggested that host factors are of less importance in metastasis.

Similar cell lines have been developed from a mouse lymphosarcoma, a system called the RAW117. In this system, the relatively non-metastatic parental line, RAW117-P, and subline RAW117-H10, selected for its high incidence of liver metastasis, can be separated by physical procedures on the basis of differences in cell-surface charge densities and hydrophobic/hydrophilic properties. Further analysis has demonstrated that the H10 line is missing a 70,000 molecular weight protein from its cell surface. Also, further, the H10's affinity for liver colonization appear related to the expression of fetal liver antigens on the fibrosarcoma cells which the hepatic tissue recognizes and tolerates. Antibodies directed against this antigen inhibit tumor implantation (Nicolson et al., 1982).

Although the B16 melanoma was a practical model in which to ask certain questions, it has been pointed out that in the whole animal, spontaneous metastases requires that cancer cells must first gain access to the blood stream. When the highly metastatic lines were compared with the low frequency metastatic lines by intramuscular administration to mice, very few metastatic foci developed at all (Stackpole, 1981). In a direct comparative study of two B16 lines (one of high and one of low metastatic ability) administered either by intravenous (i.v.) or intramuscular (i.m.) injection, results were not parallel. The F10 line produced more than 10 times the number of pulmonary tumors as the F10^{1.r-6} line, after i.v. injection. However there was no difference in the number of lung metastasis observed after i.m. administration (Weiss et al., 1983). In vitro experiments in which the sensitivity of the two melanoma lines to cytotoxicity of whole mouse blood was assessed showed that three times more F10

cells survived the blood treatment than F101.r-6 cells. This suggests then that entry into the blood may be the rate-limiting process. The F101.r-6 cells get into the circulation more easily, that is, they can penetrate the basement membranes of small veins, but once in the vessels they are more subject to the killing effects of blood. A similar study using Lewis lung carcinoma, methycholanthrene induced (MCl and MC2) fibrosarcomas and B16 melanoma cells compared the incidence of lung nodules after administration of the cells to live mice by i.v. versus i.m. injection. After i.v. injection the MCl and MC2 cells caused the largest number of pulmonary tumors, but after i.m. injection the Lewis lung carcinoma showed the highest rate of metastasis (Glaves, unpublished).

Continuous serial subcutaneous transplantation of B16 melanoma cell lines in mice also effects gradual changes in the incidence of pulmonary metastasis. Since the genetic instability of tumors has been well established it is not surprising that phenotypic expression might be dramatically and rapidly modified (Stackpole, 1983).

The phenomena of tumor cells with a prediliction for metastasis to the ovary is also seen with mouse embryonal carcinoma cell lines. After intraperitoneal, but not i.v. injection, exclusively ovarian tumors are formed. This selectivity is the result of significant adhesion of the embryonal cells to ovarian germinal epithelium. As with the fibrosarcoma cell lines, monoclonal antibodies can successfully block this adhesion. The system is especially well suited for studying tumor cell binding to surface molecules on ovarian cells or to components of the extracellular matrix (Kahan and Adamson, 1983).

Tumor Cell Heterogeneity

The most formidable obstacle to the successful treatment of cancer may well be the fact that cells of a tumor are biologically heterogeneous. This phenotypic diversity, which allows selected variants to develop from the primary tumors, means not only that primary tumors and metastases can differ in their responses to treatment but also that individual metastases differ from one another. This diversity can be generated rapidly in model systems even when the tumors originate from a single (i.e. cloned) transformed cell. One of the important goals of today's cancer research is to better understand the biological mechanisms operating in the generation of phenotypic diversity in primary and secondary neoplasms. Information in this area will be vital to our understanding of tumor progression, the loss or acquisition of various characteristics with the passage of time. We must understand why highly malignant tumor variants are more likely to undergo rapid evolution and progression than their less malignant counterparts, and we must reconcile this with the fact that different subpopulations of tumor cells act to stabilize their relative proportions and thus impose an equilibrium on the combined population. Although we know nothing about the mechanisms operating in the generation and maintenance of tumor cell heterogeneity, the process does not appear to be random but rather ordered and highly selective. Selective events are governed by rules, so we can be optimistic that the generation of tumor heterogeneity will someday be understood (Fidler and Hart, 1982).

In a recent conference on cancer invasion and metastasis (Nicolson and Milas, 1983) a number of scientists presented interesting data, some of the first to appear which attempt to explain how diversity is generated in tumor cell populations.

Cytogenetic information strongly suggested that cellular subpopulations within tumors result from discrete sequential genetic alterations that are of clonal origin. It is important to pursue these observations by mapping the loci and further investigating their function using molecular genetic methods now available. Many believe that these loci will correspond to different oncogenes which are expressed at various stages of development and differentiation. More specific studies have concentrated on using cells which have been selected for their resistance to various drugs or absence of certain surface determinants which interact with lectins. Using a transplantable, cloned mouse tumor cell line (MDW4), which had been tagged with genetic markers prior to inoculation, it was possible to establish causal relationships between the emergence of malignant properties, tumor heterogeneity and genetic constitution. Conclusions from this study clearly indicated that non-metastatic cells acquired a metastatic phenotype via fusion with a bone-marrow derived cell (probably a macrophage) followed by chromosome segregation. This may be one means by which tumors can genetically diversify, increase their ploidy, and, through selection, acquire more aggressive characteristics. Although fusion between a cancer cell and a normal cell may be one way of generating diversity, other studies using a different mouse model (Bl6) suggested that fusion between host cells and tumor cells was a very uncommon occurrence compared to fusion between different tumor cells. Clearly, any fusion between tumor cells could also generate aneuploidy and result in new tumor cell variants. In fact, the results with Bl6 mouse melanoma cell variants seem to support the conclusion that in vivo tumor cells of different invasive and metastatic characteristics can interact (probably through cell fusion) to give rise to variants of increased malignancy. Thus two separate laboratories have obtained results that cell fusion phenomenon are important to the generation of tumor heterogeneity. Interestingly, this is a revitalization of an old hypothesis which was discarded years ago when the technology of tagging mammalian cells with genetic markers was not available.

Discussion

There has been a virtual explosion of results in the last year, and we expect this rate of knowledge acquisition to continue at the same pace for many years into the future. The area with the most significant new activity was oncogene research, and results in this field have been particularly satisfying because they exemplify the importance of basic research to the solution of cancer problems. The answers that we are now getting are due to the convergence of technologies developed in the last ten years and the collaborations between scientific disciplines that previously viewed their research areas as separate and unrelated. Disparate observations are coming together into singular research problems for tumor biologists, cytogenetists, molecular geneticists, immunologists and virologist. Somatic cell hybridization technology and cytogenetic banding techniques have provided powerful tools for mapping genes to specific chromosomes. Restriction enzymes found in bacteria, which cut DNA at specific sites, and DNA recombinant techniques, which allow for the preparation and use of pure genetic probes, have provided the capability of studying mammalian DNA organization at the molecular level. Micro-techniques for DNA sequencing are providing a rapid way for comparing different sequences and predicting amino acid primary structures from the genetic code. An example of the power of this technique is the one amino acid change found for the T-24 gene product. Hybridoma technology (i.e. monoclonal antibodies) is certain to become a powerful tool for both fishing out oncogene products and studying their biological activity.

Despite all of these advancements, we still don't understand cancer as a multistep process, but we can be optimistic that the next few years will provide more exciting discoveries.

FISCAL YEAR 1983
TUMOR BIOLOGY PROGRAM

SUMMARY BY SUB CATEGORY (DOLLARS IN THOUSANDS)

	NON-COMPETING		COMPETING		TOTAL	
	No.	Amount	No.	Amount	No.	Amount
A. Cell Surface	99	\$7,653	30	\$2,966	129	\$10,619
B. Enzymes	23	2,790	11	913	34	3,703
C. Peptide Hormones	15	1,583	6	601	21	2,184
D. Steroids	20	1,976	8	927	28	2,903
E. Membrane Organelles	11	1,909	1	90	12	1,999
F. Ribosomes & Polyribomes	1	197	3	503	4	700
G. M-RNA	14	1,572	3	299	17	1,871
H. T-RNA	5	461	1	85	6	546
I. DNA	7	835	6	817	13	1,652
J. Growth Factors	23	2,803	9	915	32	3,718
K. Nucleus	14	1,357	7	777	21	2,134
L. Contractile Elements	7	759	6	579	13	1,338
M. Development & Differentiation	40	5,175	28	2,991	68	8,166
N. Cell Growth, Cell Division	21	2,176	9	774	30	2,950
P. Somatic Cell Genetics	15	1,951	1	96	16	2,047
Q. Inheritance of Neoplasms	5	462	0	0	5	462
R. Plasmids, Viruses	7	585	0	0	7	585
S. In Vivo & In Vitro Tumor Lines	9	1,077	1	59	10	1,136
W. Difficult to Classify	4	675	0	0	4	675
SUB TOTAL	340	\$35,996	130	\$13,392	470	\$49,388
V. Program Projects	12	8,628	4	2,462	16	11,090
T. Conferences	1	125	5	49	6	174
SUB TOTAL	13	\$8,753	9	\$2,511	22	\$11,264
TOTAL	353	\$44,749	139	\$15,903	492	\$60,652

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CELL SURFACE

- RO1 CA08759 Structure, Biosynthesis and Function of Glycoproteins
 Kornfeld Washington University
- RO1 CA12150 Unusual Lipids in Cancer Tissues
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R01 CA17287 Mechanism and Role of Gene Amplification in Mammals
Stark Stanford University

R01 CA23365 DNA Polymerases in Normal and Cancer Cells
Chang U.S. Uniformed Services Univ. of Hlth. Sci.

R01 CA24158 Rates of DNA Synthesis in Normal and Transformed Cells
Collins Virginia Commonwealth University

R01 CA24845 The Fidelity of DNA Replication in Human Lymphocytes
Loeb University of Washington

R01 CA26391 Molecular Pathology of Leukemia and Lymphoma
Coleman University of Kentucky

R23 CA30387 Deoxyribonucleoside Triphosphate Metabolism
Albert Dana-Farber Cancer Institute

R01 CA34784 The Molecular Genetics of DHFR Gene Expression
Melera Sloan Kettering Institute for Cancer Research

R23 CA34898 Cytoskeletal and Membrane Associations of B Cell IG
Rosenspire Sloan Kettering Institute for Cancer Research

R23 CA35703 Cytoplasmic Control of Normal and Neoplastic Cell Growth
Gutowski University of Connecticut

GROWTH FACTORS

R01 CA02146 Cytoplasmic Factors in Cellular Growth
Bucher Massachusetts General Hospital

R01 CA11176 Factors Required for Mammalian Cell Division
Holley Salk Institute for Biological Studies

R01 CA14019 Tumor Angiogenesis: A Control Point in Tumor Growth
Folkman Children's Hospital Medical Center

R01 CA15744 Spontaneous Transformation and Progression in Cell Lines
Rubin University of California, Berkeley

R01 CA17620 Growth Control in Normal and Neoplastic Cells
Smith University of Nebraska, Lincoln

R01 CA19275 Normal and Leukemic Granulopoiesis
Dodge Wake Forest University

R01 CA19731 Human Tumor Culture Lines in Defined Media
Sato University of California, San Diego

R01 CA21763 Cartilage and Chondrosarcoma-Derived Growth Factors
Klagsbrun Children's Hospital Medical Center

R01 CA22410 Ceruloplasmin and Copper Metabolism in Cancer
Linder California State University, Fullerton

R01 CA24071 Studies of the Receptor for Epidermal Growth Factor
Carpenter Vanderbilt University

R01 CA25820 Receptors and Growth Factors for Neoplastic Cells
Schlessinger Weizmann Institute of Science

R01 CA27217 Growth Factors and Receptors in Chemical Transformation
Moses Mayo Foundation

R01 CA27466 Endothelial Colony-Stimulating Activity
Quesenberry University of Virginia, Charlottesville

R23 CA27802 Pharmacologic Modulation of Erythroid Colony Formation
Beckman Tulane University

R01 CA28110 Nerve Growth Factor Function--Secretion by Cancer Cells
Young University of Florida

R01 CA28540 Growth and Migration of Capillary Endothelial Cells
Zetter Children's Hospital Medical Center

R01 CA28858 Biological and Synthetic Modulators of Cell Growth
Pickart Virginia Mason Research Center

R01 CA29101 Characterization of a Liver Specific Growth Promotor
La Brecque University of Iowa

R01 CA30101 Structure and Function of Platelet-Derived Growth Factor
Antoniades Center for Blood Research

- R01 CA30479 Mononuclear Phagocyte-Derived Growth Regulating Factors
Gillespie University of North Carolina, Chapel Hill
- R01 CA30536 New Myeloid Hemopoietins: Normal and Leukemic Marrow
Wells University of California, Los Angeles
- R01 CA31279 Epidermal Growth Factor: Interactions with Cell Receptor
Haigler University of California, Irvine
- R01 CA31529 The Hormonal Regulation of Normal Cell Growth
Rossow Jackson Laboratory
- R01 CA31615 Growth Factors in Normal and Neoplastic Hematopoiesis
Adamson University of Washington
- R01 CA31796 Effect of Glia Maturation Factors on Tumors
Lim University of Iowa
- R01 CA34162 Growth Factors and Cellular Transformation
Scher Children's Hospital of Philadelphia
- R01 CA34470 The Role of Epibolin and Serum in Cancer Cell Spreading
Stenn Yale University
- R01 CA34568 Control of Tumor-Induced Vascularization
Fenselau Miami Heart Institute
- R23 CA34590 Biochemistry of a Melanoma Growth Stimulation
Richmond Emory University
- R01 CA34610 Intracellular Targets of Transforming Growth Factors
Massague University of Massachusetts Medical School
- R01 CA35373 Hepatopoietins, Liver Regeneration and Carcinogenesis
Michalopoulos Duke University
- R01 CA36740 Regulation of Myelopoiesis by Acidic Isoferritins
Broxmeyer Indiana University Foundation

NUCLEUS

- R01 CA12226 Metabolism of NC-Methylarginines and Neoplasia
Paik Temple University
- R01 CA13195 Histone ADP-Ribosylation and HeLa Cell Replication
Smulson Georgetown University
- R01 CA16346 Molecular Control of Chromatin Transcription
Axel Columbia University

R01 CA16910	Chromosome Aberrations in Myeloproliferative Diseases
Rowley	University of Chicago
R01 CA17782	Tumor-Enriched Nonhistone Chromatin Proteins
Reeck	Kansas State University
R01 CA18455	Isolated Chromosomes in Genetics and Cancer Research
Wray	Baylor College of Medicine
R01 CA21927	Chromatin Structure of Normal and Malignant T Cells
Maizel	University of Texas System Cancer Center
R01 CA24546	Relation of Histones to DNA in Normal and Cancer Cells
Kornberg	Stanford University
R01 CA25055	Cytogenetics of Clonal Neoplasias
Hecht	Southwest Biomedical Research Institute
R01 CA27661	Sister Chromatid Exchange in ALL
Palmer	Indiana Univ.-Purdue Univ. at Indianapolis
R01 CA29340	rDNA Distribution in Chromosomes of Neoplastic Cells
Henderson	Columbia University
R01 CA29476	Clonal Karyotypic Evolution in Human Solid Tumors
Trent	University of Arizona
R01 CA31024	Fine Structural Chromosomal Defects in Acute Leukemia
Yunis	University of Minnesota of Minneapolis-St. Paul
R01 CA33011	Chromatin Proteins of Embryonal Carcinoma Cells
Oshima	La Jolla Cancer Research Foundation
R01 CA33314	Fine Chromosomal Defects in Non-Hodgkin's Lymphoma
Yunis	University of Minnesota of Minneapolis-St. Paul
R01 CA34003	Nuclear cAMP Binding Proteins in Morris Hepatomas
Rosenberg	Albany Medical College of Union University
R01 CA34462	Role of Double Minutes and HSR Markers in Tumor Cells
George	University of Pennsylvania
R01 CA34775	Mapping Chromosomes and Genes in Relation to Leukemia
Chaganti	Sloan Kettering Institute for Cancer Research
R01 CA34783	Monoclonal Antibodies to Mitotic Cells
Rao	University of Texas System Cancer Center
R23 CA34831	Gene Mapping of Chromosome 3 and Small Cell Carcinoma
Miller	University of Colorado Health Sciences Center
R01 CA35829	Histone in Virally-Infected and Transformed Cells
Jackson	Medical College of Wisconsin

CONTRACTILE ELEMENTS

- | | | |
|-------------|---|---|
| R01 CA05493 | Leukopoietic Mechanisms
De Bruyn | University of Chicago |
| R01 CA15544 | Effect of Microtubular Proteins on Cell Surfaces
Berlin | University of Connecticut Health Center |
| R01 CA22031 | Trans-Membrane Control in Transformed and Normal Cells
Singer | University of California, San Diego |
| R01 CA23022 | Studies of Mitosis in Normal and Neoplastic Cells
Brinkley | Baylor College of Medicine |
| R01 CA29405 | Studies on Prostacyclin and Tumor Metastasis
Honn | Wayne State University |
| R01 CA29985 | Microtubules and Nonmicrotubular Aggregates
Weisenberg | Temple University |
| R23 CA31460 | Contractile Protein Function in Normal and Transformed Cells
Kiehart | Johns Hopkins University |
| R01 CA31760 | Intermediate Filaments in Normal and Transformed Cells
Goldman | Northwestern University |
| R01 CA33265 | Tropomyosin and Stress Fibers: Transformed Cells
Warren | University of Miami |
| R01 CA34155 | Movement of Virus-Transformed Cell Cytoplasm
Albrecht-Buehler | Northwestern University |
| R01 CA34709 | Lymphoma Metastasis/Role of Endothelial Cell Recognition
Butcher | Stanford University |
| R01 CA35738 | Tropomyosins in "Normal" and Transformed Cells
Matsumura | Cold Spring Harbor Laboratory |
| R23 CA35954 | Cytochalasin/Probes of Cytoskeletal Function
Krafft | Syracuse University |

DEVELOPMENT AND DIFFERENTIATION

- | | | |
|-------------|---|-----------------------------------|
| R01 CA02662 | Investigations on Teratocarcinogenesis
Stevens | Jackson Laboratory |
| R01 CA10095 | Gene Action and Cellular Differentiation in Culture
Silagi | Cornell University Medical Center |

R01 CA13047 Control Mechanisms of Differentiation and Malignancy
Friend Mount Sinai School of Medicine

R01 CA13533 Ectopic Placental Proteins in Cancer
Sussman Stanford University

R01 CA14054 Malignant Behavior and Cellular Antigen Expression
Klein Caroline Institute

R01 CA14319 Glycoconjugates and Nervous System Cell Differentiation
Schengrund Pennsylvania State University Hershey Medical Center

R01 CA15222 Hepatoma AFP: Model of Glycosylation in Malignancy
Smith University of Vermont and State Agriculture College

R01 CA15619 Normal and Malignant Hematopoietic Cell Replication
Cline University of California, Los Angeles

R01 CA16368 Control of Differentiation of Erythroleukemic Cells
Skoultchi Yeshiva University

R01 CA16720 Gene Regulation and Interaction--Normal and Malignant Cell
Klinger Yeshiva University

R01 CA17389 C-Cell Hyperplasia and Medullary Thyroid Carcinoma
Wolfe Tufts University

R01 CA17575 Erythroid Differentiation in Friend Leukemia Cells
Housman Massachusetts Institute of Technology

R01 CA19492 Terminal Transferase in Mammalian Hemopoietic Tissue
Coleman University of Kentucky

R01 CA21967 Normal/Neoplastic Phosphatases: Comparative Structures
Fishman La Jolla Cancer Research Foundation

R01 CA22294 Quantitative Studies on Granulocyte Differentiation
Kinkade Emory University

R01 CA22556 Differentiation of Granulocytes and Macrophages
Metcalf Walter and Eliza Hall Institute of Medical Research

R01 CA22735 Thymic Modification of Leukemogenesis
Sensenbrenner Johns Hopkins University

R01 CA23097 Embryo-Derived Teratocarcinoma
Damjanov Hahnemann University

R01 CA24241 Differentiation in a Malignant Neural Tumor
Pantazis University of Iowa

R01 CA24479 Polyamine Metabolism and Neuroblastoma Differentiation
Chen Rutgers, The State University, New Brunswick

R01 CA24488 The Controlled Initiation of Neoplasms in Drosophila
Hanratty University of California, Irvine

R01 CA25098 Alpha-Fetoprotein Regulation in Fetal and Cancer Liver
Chiu University of Vermont and State Agriculture College

R01 CA25512 Modulators of Granulopoiesis from Human Cell Lines
Brennan University of Rochester

R01 CA25966 X-Chromosome Activity in Teratocarcinoma Stem Cells
Martin University of California, San Francisco

R01 CA25972 Self-Renewal in Normal/Leukemic Hemopoietic Stem Cells
Metcalf Walter and Eliza Hall Institute of Medical Research

R01 CA26038 Differentiation and Proliferation of Myeloid Cells
Koeffler University of California, Los Angeles

R01 CA26656 Cell Culture Analysis of Human Epithelial Neoplasia
Rheinwald Dana-Farber Cancer Institute

R01 CA28050 Regulation of Alpha-Fetoprotein Gene Expression
Tilghman Institute for Cancer Research

R23 CA28289 Nuclear vs. Extranuclear Control of Gene Expression
Moore University of Colorado Health Sciences Center

R01 CA28427 EGF and Its Receptors in Embryonic Differentiation
Adamson La Jolla Cancer Research Foundation

R01 CA28656 Differentiation of Capillary Endothelial Cells
Auerbach University of Wisconsin, Madison

R01 CA29169 Gene Expression Embryonal Carcinoma Differentiation
Linney La Jolla Cancer Research Foundation

R01 CA29894 Human Teratocarcinoma-Derived Cell Lines
Andrews Wistar Institute of Anatomy and Biology

R01 CA29895 Antiproliferative Effects of Interferons
Baglioni State University of New York at Albany

R01 CA30049 Oncofetal Gene Regulation in Hepatocarcinogenesis
Papaconstantinou University of Texas Medical Branch, Galveston

R01 CA30684 Regional Differences in Tumor Growth and Development
Auerbach University of Wisconsin, Madison

R01 CA31042 Developmental Regulation of B Globin Gene Expression
Lo University of Pennsylvania

R01 CA31271 Differentiation and Stroma-Induction in Neural Tumors
Rubinstein University of Virginia, Charlottesville

P01 CA31768 Leukemia Cell Systems: Induction of Differentiation
Rifkind Sloan Kettering Institute for Cancer Research

R01 CA31937 Control of Melanoma Cell Differentiation: Genetic Study
Graf Cornell University Medical Center

R01 CA31945 K-562: A Human Pluripotent Leukemia Stem Cell Line
Lozzio University of Tennessee, Knoxville

R01 CA32152 Growth and Differentiation of Human Melanocytes
Eisinger Sloan Kettering Institute for Cancer Research

R01 CA32186 REC-DNA Analysis of Human Hematopoietic Differentiation
Salser University of California, Los Angeles

R23 CA32260 Differentiation and Malignancy in Neural Cell Culture
Krystosek University of Colorado Health Sciences Center

R01 CA32586 Myeloid Development in an Induced Leukemic Cell Line
Cohen University of Rochester

R23 CA32733 Modulation of Normal and Abnormal Human Myelopoiesis
Abraham University of Pennsylvania

R01 CA33000 Glycoproteins in Differentiation and Oncogenesis
Fukuda La Jolla Cancer Research Foundation

R01 CA33021 Isolation of Tumor Genes from Human Lung Carcinomas
Perucho State University of New York, Stony Brook

R01 CA33065 Immunobiology of UVL-Induced Tumors
Daynes University of Utah

R01 CA33579 Growth and Differentiated Function of Keratinocytes
Green Harvard University

R01 CA33664 The In Vitro and In Vivo Regulation of Hemopoiesis
Cronkite Associated University-Brookhaven National Laboratory

R01 CA33800 Pathobiology of Chemically Induced Teratocarcinoma
Speers University of Colorado Health Sciences Center

R01 CA33895 Glycoproteins in Normal and Leukemic Cell Differentiation
Fukuda La Jolla Cancer Research Foundation

R01 CA33946 Teratocarcinoma Cytoskeletal Proteins
Oshima La Jolla Cancer Research Foundation

R01 CA34181 RNA's of Lymphoma and T Cell Differentiation Antigens
Rothenberg California Institute of Technology

R23 CA34186 Human Immature Megaleryocytes and Hematologic Neoplasms
Long University of Michigan at Ann Arbor

R01 CA34230 Onco-Developmental Gene Control: Alpha-Fetoprotein
Sell University of Texas Health Science Center, Houston

R01 CA34291 Developmental Variants of Embryonal Carcinoma Cells
Moore University of Colorado

R01 CA34759 Molecular Basis of Oncogenesis and Differentiation
Tereba St. Jude Children's Research Hospital

R01 CA34772 DNA Rearrangements at the MYC Locus in Myeloma Tumors
Cole St. Louis University

R01 CA34826 Oncogenes and Growth Factors in Pre-B Cells
Ozanne University of Texas Health Science Center, Dallas

R01 CA34891 Molecular Basis of Differentiation and Neoplasia
Roeder Rockefeller University

R01 CA35150 Chromosome Translocations and IG Genes in Human Leukemia
Nowell University of Pennsylvania

R01 CA35326 Expression of Exogenous Genes in Teratocarcinoma
Gautsch Scripps Clinic and Research Foundation

R01 CA35367 Embryonic Control of Neuroblastoma and Melanoma
Pierce University of Colorado

R01 CA35517 The Role of cAMP in Leukemic Cell Differentiation
Fontana West Virginia University

R01 CA35823 Human Lymphocytic Leukemia Oncogenes/Gene Products
Kennett University of Pennsylvania

R01 CA36122 Neuroblastoma Transfection and Transformation
Gilbert Mount Sinai School of Medicine

CELL GROWTH, CELL DIVISION

R01 CA06663 Mechanisms of Control of Mammalian Cell Multiplication
Lieberman University of Pittsburgh

R01 CA15062 Studies of Normal and Neoplastic Prostate
Ahmed University of Minnesota of Minneapolis-St. Paul

R01 CA15141 Control of Nuclear Events in Normal and Neoplastic Cells
O'Neill University of Utah

R01 CA15305 Effect of Malignancy on Cell Growth Requirements
Ham University of Colorado at Boulder

R01	CA15813 Baker	Lipid Transport and Metabolism in Cancer-Host Systems University of California, Los Angeles
R01	CA16463 Surks	Thyroid Hormone Effects on Cell Regulation Montefiore Hospital and Medical Center
R01	CA16816 Moses	Mechanism of Chemical Carcinogenesis In Vitro Mayo Foundation
R01	CA22042 Stiles	Molecular Analysis of Progression Through G1 Dana-Farber Cancer Institute
R01	CA24193 Pledger	Regulation of Mammalian Cell Cycle University of North Carolina, Chapel Hill
R01	CA24385 Mastro	Effects of Phorbol Esters on Lymphocyte Stimulation Pennsylvania State University, University Park
R01	CA25898 Baserga	Analysis of G1 in Mammalian Cells Temple University
R01	CA26070 Basilico	Control of Cycle Progression in Animal Cells New York University
R01	CA26081 Varga	Cell Cycle Dependence of Cell Surface Receptors Yale University
R01	CA27399 Sisken	Regulation of Mitosis in Normal and Transformed Cells University of Kentucky
R01	CA27544 Rao	Purification and Characterization of Mitotic Factors University of Texas System Cancer Center
R01	CA27564 Hoffman	Methionine Dependence--A Metabolic Marker in Cancer University of California, San Diego
R01	CA28238 Vogel	Effects of Mitogens on Normal and Neoplastic Cells University of Washington
R01	CA28240 Scott	Pathology in Cell Cycle Control of Differentiation Mayo Foundation
R01	CA28519 Rosenblum	Characterization of Cells and Clones from Human Brain University of California, San Francisco
R01	CA28760 Hauschka	Anticoagulants, Vitamin K, and Tumor Cell Growth Children's Hospital Medical Center
R01	CA28803 Rapaport	The Role of Nucleotides in Malignant Transformation Boston University
R01	CA30083 Eisenstein	Aortic Growth Inhibitors Mount Sinai Medical Center

R01 CA31053 Mitotic Inducing Protein(s) from Mammalian Cells
Vogelstein Johns Hopkins University

R01 CA32094 Humoral Control of Leukemic Blast Proliferation
Taetle University of California, San Diego

R01 CA32172 Regulation and Inhibition of Polyamine Metabolism
Hoffman University of Louisville

R01 CA32952 Phosphotyrosine and the Control of Cell Growth
Ross Wistar Institute of Anatomy and Biology

R01 CA33505 Cell Cycle Specific Control of Cellular Differentiation
Yen University of Iowa

R01 CA34512 Regulation of 2-5A-Dependent RNase Levels By Interferon
Silverman U.S. Uniformed Services Univ. of Hlth. Sci.

R01 CA35469 Collagenase Function and Activity in Malignant Tumors
Takahashi Yeshiva University

R01 CA35789 Regulation of Gene Expression by Interferons
Sen Sloan Kettering Institute for Cancer Research

SOMATIC CELL GENETICS

R01 CA12130 Cytoplasmic Inheritance in Normal and Tumor Cells
Harris University of California, Berkeley

R01 CA16631 Epithelial Cell Growth and Function: A Genetic Study
Meiss New York University

R01 CA16754 Hybridization, DNA Function, Mutation in Cell Culture
Littlefield Johns Hopkins University

R01 CA19401 Genetic Analysis of Human Malignancy
Stanbridge University of California, Irvine

R01 CA20741 Biology of Human Fibrosarcoma
Croce Wistar Institute of Anatomy and Biology

R01 CA21054 Genetic Analysis of Malignant Transformation
Shin Yeshiva University

R01 CA24828 Genetic Analysis of Tumorigenesis
Sager Dana-Farber Cancer Institute

R01 CA28559 Study of Malignant Transformation: A Genetic Analysis
Athwal University of Medicine & Dentistry of New Jersey

R01 CA30643 Genetic Bases for the Transformed Phenotype
Ozer Hunter College

R01 CA30938 Structural and Functional Analysis of Cloned MHC Gene
Weissman Yale University

R01 CA31553 Cytogenetics and Molecular Biology of Human Neuroblastoma
Biedler Sloan Kettering Institute for Cancer Research

R01 CA31649 Transformation Proteins of Non-Virally Induced Tumors
Weinberg Massachusetts Institute of Technology

R01 CA31777 BUDR Dependence, Malignancy, and Differentiation
Davidson University of Illinois at Chicago

R01 CA31995 Retroviral Oncogenes: Analysis of Cellular Homologues
Sheiness Louisiana State Univ. Med. Ctr., New Orleans

R01 CA32580 Biochemical Genetics of Mammalian Nucleoside Transport
Ullman University of Kentucky

R01 CA33108 Cell Transforming Genes of T- and B-Lymphocyte Neoplasms
Lane Dana-Farber Cancer Institute

INHERITANCE OF NEOPLASMS

R01 CA29078 Cellular Origins of Rat Hepatic Preneoplasias
Iannaccone Northwestern University

R01 CA32832 Cytogenetics of Familial Medullary Thyroid Carcinoma
Wurster-Hill Dartmouth College

R01 CA33093 Recombinant Inbred Mouse Strains and Cancer
Taylor Jackson Laboratory

R01 CA33383 Transforming Genes of Benign and Malignant Colon Tumors
Augenlicht Sloan Kettering Institute for Cancer Research

R23 CA33947 Analysis of Genetic Heterogeneity in Fanconi Anemia
Auerbach Rockefeller University

PLASMIDS, VIRUSES

R01 CA11526 Tumor-Inducing Substance of Agrobacterium Tumefaciens
Kado University of California, Davis

R01 CA18604 The Mechanism of Tumorigenesis by A. Tumefaciens
Matthysse University of North Carolina, Chapel Hill

R01 CA19402 Molecular Genetics of Agrobacterium Plasmids
 Farrand Loyola University Medical Center

R01 CA26963 Molecular Regulation of Crown Gall Tumor Growth
 Chang University of Wisconsin, Parkside

R01 CA28946 Transfection by Endogenous Human Transforming Genes
 Cooper Dana-Farber Cancer Institute

R01 CA29474 Cytology, Biochemistry of Viral-Specific Proteins
 Buchanan Massachusetts Institute of Technology

R01 CA34171 Analysis of Malignancy by Gene Transfer
 Kucherlapati University of Illinois at Chicago

IN VIVO AND IN VITRO TUMOR LINES

R01 CA11683 Coenzymes and Nucleic Acids Metabolism
 Kaplan University of California, San Diego

R01 CA17229 Keloids: An In Vitro Model of Tumor Growth Regulation
 Russell Meharry Medical College

R01 CA24145 Ovarian Tumors in Young Mice
 Beamer Jackson Laboratory

R01 CA28668 Biologic Markers for Melanoma
 Gehrke University of Missouri, Columbia

R01 CA29440 Biochemical Identification of Organ Specific Melanoma
 Mehard University of California, San Francisco

R01 CA30082 Genetics and Development of Teratocarcinoma Cells
 Nesbitt University of California, San Diego

R01 CA30621 Biology and Immunobiochemistry of Hematopoietic Tumors
 Epstein Northwestern University

R01 CA32134 B16 Melanoma Metastasis Model System
 Stackpole New York Medical College

R01 CA32318 Antigenic Analysis of Hematopoiesis
 Civin Johns Hopkins University

R01 CA33027 Differentiation and Chemotherapy in Human Gliomas
 Yung University of Texas System Cancer Center

CONFERENCES

- R13 CA16224 Support for Cancer Research Center Workshops
Grodzicker Cold Spring Harbor Laboratory
- R13 CA30001 Cold Spring Harbor Conferences on Cell Proliferation
Watson Cold Spring Harbor Laboratory
- R13 CA30245 1983 Annual Symposium on Fundamental Cancer Research
Lemaistre University of Texas System Cancer Center
- R13 CA34190 Conference on Normal and Neoplastic Hematopoiesis
Fox University of California, Los Angeles
- R13 CA35846 Gordon Research Conference on Cancer, 1983
Kripke Gordon Research Conferences

PROGRAM PROJECTS

- P01 CA10893 Cancer Research Center
Busch Baylor College of Medicine
- P01 CA12923 A Correlated Study on the Biology of Neoplasia
Baserga Temple University
- P01 CA14454 The Plasma Membrane in Normal and Cancer Cells
Racker Cornell University
- P01 CA15823 Program in Developmental Biology of Cancer
Pierce University of Colorado Health Sciences Center
- P01 CA19265 Chromosome Metabolism in Cancer Biology
Ultmann University of Chicago
- P01 CA21901 Studies of Normal and Malignant Cell Membranes
Roseman Johns Hopkins University
- P01 CA22376 Control of Gene Expression: Normal and Neoplastic
Feigelson Columbia University
- P01 CA22427 Molecular Analysis of Malignant Transformation
Pardee Dana-Farber Cancer Institute
- P01 CA23052 Program Project on Athymic Mice and Human Tumors
Kaplan University of California, San Diego
- P01 CA23076 Regulatory Mechanisms in Tumor Biology
Mueller University of Wisconsin, Madison

- P01 CA25845 Pathobiology of Small Cell Carcinoma of the Lung
Sorenson Dartmouth College
- P01 CA25875 Cell Differentiation and Cancer
Croce Wistar Institute of Anatomy and Biology
- P01 CA26712 Molecular Analyses of Cellular Proteins and Their Genes
Hynes Massachusetts Institute of Technology
- P01 CA28853 Pathophysiology of Metastasis
Holyoke Roswell Park Memorial Institute
- P01 CA28896 Cell-Matrix Interactions in Neoplasia and Development
Ruoslahti La Jolla Cancer Research Foundation
- P01 CA29545 Interferon, Differentiation and Oncogenesis
Carter Hahnemann Medical College & Hospital of Philadelphia
- P01 CA29569 Gene Organization and Expression in Eukaryotes
Watson Cold Spring Harbor Laboratory
- P01 CA32737 Medical Oncology
Golde University of California, Los Angeles

DIFFICULT-TO-CLASSIFY

- R01 CA09247 Partial Subsidy for the Journal of Cancer Research
Handschumacher American Association for Cancer Research
- R01 CA22062 A Bone Resorptive Protein from Cancer Ascites Fluid
Nimberg Boston University
- R01 CA25298 Biology of Human Cutaneous Malignant Melanoma
Clark University of Pennsylvania
- R01 CA27120 Interferon System: Action, Induction and Regulation
Ts'0 Johns Hopkins University

CONTRACT RESEARCH SUMMARY

Title: Morris Hepatoma Resource Program

Principal Investigator: Dr. Wayne E. Criss
Performing Organization: Howard University College of Medicine
City and State: Washington, D.C.

Contract Number: N01-CB-14345
Starting Date: 7/1/81 Expiration Date: 6/29/84

Goal: To maintain eleven Morris hepatomas representative of the spectrum of rapidly to very slow-growing tumors in stock rats and provide them on request to laboratories for research purposes.

Approach: The hepatomas are propagated by serial transplantation in rats and periodically monitored by enzyme profiles and assay of specific metabolites to assure stability of each line. Requests for any of the hepatomas are filled, depending on availability, by injecting tumor tissue into host rats purchased by the requestor and then shipping them to his/her laboratory by air freight.

Progress: Since the inception of the contract 4291 tumor-rats and 191 controls were supplied to investigators on request. The actual use is broken down as follows:

<u>Fast-growing</u>	<u>Tumor-Rats</u>	<u>Slow-Growing</u>	<u>Tumor-Rats</u>
5123tc	223	9618A	313
7777	519	7787	86
3924A	1701	16	126
44	329	20	169
8999	122		

Intermediate-Growing

7800	507		
5123D	196	Controls (Non-tumor-bearing)	191

Tumor-bearing rats have been sent to approximately 65 different investigators, in the U.S., Canada and Europe.

Significance to Cancer Research: Each of these hepatomas has specific characteristics that make it the tumor of choice for certain research projects. A number of NCI grants in the areas of enzymology, intermediary metabolism and molecular biology depend upon this liver tumor system.

Project Officer: Judith M. Whalen
Program: Tumor Biology Section
FY 83 Funds: \$71,467

B

IMMUNOLOGY PROGRAM

The Immunology Program of the National Cancer Institute supports research that contributes to an understanding of the role of the immune system in the development, growth and spread of tumors. The specific areas of investigation supported by the Program include:

- ° The synthesis and structure of myeloma proteins in animals and man.
- ° The synthesis, structure, and function of antibodies capable of reacting with tumor cells, agents which induce tumors, and agents used in the treatment of tumors.
- ° The synthesis, structure, and function of humoral factors other than antibody which participate in, activate and/or regulate the immune response to tumors. This would include complement, interferon, lymphokines, lymphoid cell growth factors, helper factors, suppressor factors, etc., as they are involved in immune responses to tumors.
- ° The immunobiology of lymphocytes which participate in antitumor responses including their development, heterogeneity, interactions, and functions.
- ° The immunobiology of monocytes and macrophages which participate in antitumor responses including their development, heterogeneity, interactions, and functions.
- ° The identification, isolation, and characterization of cell surface determinants of lymphocytes and macrophages which are involved in the responses of these cells to tumors.
- ° The identification, isolation, and characterization of cell surface determinants on tumor cells which serve as target antigens for the immune response.
- ° The immunobiology of malignancies of the immune system (lymphomas and leukemias) including studies of immunologic markers for the classification and characterization of neoplastic cells and their normal counterparts.

- ° Immunobiology of sarcomas, carcinomas, and melanomas including studies of immunologic markers for the classification and characterization of tumor cells and their normal counterparts.
- ° Immune surveillance against the development of tumors of various origins by all immune mechanisms (e.g. T cell immunity, macrophage reactivity, natural killer cell activity).
- ° Immunopathology studies on the host-tumor interaction.
- ° Immune status of tumor-bearing animals and man including studies on immunostimulation, immunosuppression, and the effects of disease course on immune function.
- ° Bone marrow transplantation (BMT) in man and animals as a treatment for cancer when the emphasis is on understanding how BMT affects or is affected by the immune system.
- ° Immunotherapy in animal models including studies on specific and non-specific stimulation of the immune system using natural and synthetic agents when the emphasis is on understanding how the therapy affects or is affected by the immune system.
- ° Immunotherapy including preclinical and clinical protocols where the main emphasis is upon the study of immune parameters, immune mechanisms, and other immunologic concerns rather than upon a therapeutic result. Included are studies on specific and nonspecific stimulation of the immune system using natural and synthetic agents.

The Immunology Program supports a broad spectrum of immunologic research. The number of grants funded in each category with their costs are identified in Table 1 of this report. Since the Immunology Program funded 438 grants and expended approximately 54 million dollars during FY 1983, this report serves to highlight selected areas of research and should not be considered comprehensive. Four areas of research have been selected. The first describes the research on the Acquired Immune Deficiency Syndrome (AIDS) and includes research on related immunologic problems. AIDS research is specifically highlighted due to its current importance as a public health problem. The second area describes selected research into the molecular regulation of the immune system. The third topic relates progress in studies on human tumor associated antigens (TAA), and the last describes research in the area of molecular genetics as it relates to immunology.

Acquired Immune Deficiency Syndrome (AIDS)

In 1981 the first reports appeared describing an acquired immune deficiency syndrome (AIDS) characterized by severe opportunistic infection associated with immunodeficiency in young homosexual males between the ages of 20-35, particularly those with a history of multiple sexual partners and recreational drug use. Some of these patients developed Kaposi's sarcoma in a virulent form quite different from the indolent form described in older men of Mediterranean origin. The salient features of this syndrome include immune dysfunction associated with anergy to recall skin test antigens, lymphopenia, diminished lymphocyte blastogenic responses, decreased numbers of helper T cells, and an inverted ratio of helper to suppressor T cells. Now, in 1983, as an increasing number of cases continue to be reported, it has become clear that this immune deficiency is, to date, irreversible and only a small number of patients have survived more than two years after diagnosis of the disease.

Evan Hersh, Roger Rossen and colleagues (CA 34674, CA 20543) are studying the nature of the immunologic defect in AIDS patients. They evaluated a group of young homosexual men who had the prodrome to the syndrome, which included a history of multiple sexual partners and multiple sexually transmitted diseases and, in addition, a past history of mild to moderate viral, bacterial, parasitic or fungal infections and had used recreational drugs. Included in this group were five men with Kaposi's sarcoma. Compared to a group of normal heterosexual individuals, the homosexual men were found to have defective immune responses, decreased numbers of helper T cells, inverted helper to suppressor T cell ratios and an elevated serum thymosin alpha-1 level, suggesting that the immunologic defect precedes the syndrome. The five patients with Kaposi's sarcoma were found to be more severely immunodeficient than the other AIDS patients without cancer, suggesting that the immune suppression by the malignant disease is superimposed on the pre-existing immune deficiency (Reuben et al., 1983). Many of the patients with the prodrome of AIDS have functionally active suppressor cells and it appears that it is the relative proportion of helper to suppressor cells, not the absolute numbers of the latter, which determines functional suppressor cell activity (Hersh et al., 1983a). In addition, Dr. Hersh and colleagues have studied the effects of isobutyl nitrite on various in vitro parameters of leukocyte function. Their experimental results suggest that isobutyl nitrite has non-specific cytotoxicity for various cells in vitro and could have immunosuppressive effects on tissues exposed in vivo during its recreational use. They speculate that these immunosuppressive effects, combined with the ability of nitrites to convert amines to nitrosamines, may be related to the development of opportunistic infections and Kaposi's sarcoma in homosexuals who use this agent (Hersh et al., 1983b). Dr. Hersh and colleagues realize that the relationship of these findings to the development or manifestation of either opportunistic infection or cancer in these patients is not known at present and they plan to continue long term follow-up of the patients.

In his studies of cell-mediated immunity, Fred Valentine (CA 19529) has observed that the helper T cells of normal heterosexual individuals may be greatly decreased in number during the course of virus infections; however, on an individual cell basis, these cells still demonstrate immunologic reactivity. In marked contrast, lymphocytes from the majority of AIDS patients have no proliferative response when stimulated by microbial antigens in vitro, even though they clearly

have been exposed in vivo to these antigens. Dr. Valentine is investigating the nature of this defect. In addition he has recently succeeded in establishing and immunologically characterizing cell lines from the blood of 8 of 13 patients with AIDS (homosexuals and addicts, including a female). Some of the cell lines have been growing in vitro for five months and all are of the same surface phenotype. Their ability to establish the same type of cell line from many AIDS patients, but not from clinically normal individuals, suggests an association of these cells with AIDS (Valentine et al., manuscript in preparation).

Other investigators also have been studying AIDS/Kaposi's sarcoma as an adjunct to previously established studies. Susan Zolla-Pazner and collaborators (CA 15585, CA 16247) have been studying the immunologic abnormalities in homosexual men to determine the relationship of these abnormalities to the development of Kaposi's sarcoma. Studies were performed to define the immunologic status of various groups of homosexual men with Kaposi's sarcoma, healthy homosexual men of similar age to the homosexual patients with Kaposi's sarcoma, and homosexual men with hyperplastic lymphadenopathy. Heterosexual men with Kaposi's sarcoma were also studied. Significant immunologic abnormalities were observed in all three groups of homosexuals studied and were most severe in those with Kaposi's sarcoma, somewhat less severe in homosexual men with lymphadenopathy and least marked but still significant in healthy homosexual men. These abnormalities were even more marked in homosexuals with opportunistic infections while heterosexual men with Kaposi's sarcoma displayed essentially normal immunologic profiles (Stahl et al., 1982). This apparent progression suggests that these various disease states may exaggerate pre-existing immune defects and/or that different degrees of immunologic aberrations predispose to one or the other of the diseases observed in this population. Although other predisposing factors are undoubtedly related to the incidence of this disease, such as the increased frequency of HLA-DR5 in both homosexual and heterosexual men with Kaposi's sarcoma, the immunologic differences between these two groups of patients might explain the difference in the course of the disease in heterosexual and homosexual men (Friedman-Kien et al., 1982). These data do not rule out, however, an involvement of infectious agents or extensive drug use in the etiology of this disease.

In studies of immunosuppressants and lymphocyte function, Alan Winkelstein and collaborators (CA 24429) have found reduced T cell colony growth in lymphocytes from patients with active systemic lupus erythematosus and a minimal reduction in T cell colony numbers in cells from patients with either progressive systemic sclerosis or rheumatoid arthritis (Winkelstein et al., 1982). In the context of these studies, they have studied lymphocytes of AIDS patients and all showed depressed T cell colony growth when stimulated in the same way with phytohemagglutinin and then plated in soft agar (unpublished data).

It is noteworthy, particularly in view of the current interest in the association of human T-cell leukemia-lymphoma virus (HTLV) with AIDS, that Richard Edelson and colleagues (CA 20499) have developed monoclonal antibodies BE1 and BE2 which react with cutaneous T-cell lymphoma (CTCL) cells from a majority of CTCL patients and not with normal lymphocytes or tissue elements. These monoclonal antibodies do react with some B cell CLL lymphocytes and some Epstein-Barr virus transformed B cell lines. They were produced against CTCL cells which were later shown to release a type-C virus identified as HTLV following long term culture in the laboratory of Dr. Robert Gallo, NCI, NIH. HTLV-transformed cell lines express a membrane antigen reactive with BE2 (Berger et al., 1982a,b).

Dr. Edelson and colleagues have found that OKT4⁺ cells of AIDS patients who have a demonstrable population of OKT4⁺ cells react with monoclonal antibody BE2. As the disease progresses, this cell population loses reactivity with BE2 (Berger et al., submitted for publication).

Also bearing on the association of HTLV with AIDS is the finding by Richard Olsen and colleagues (CA 31547) that ultraviolet-irradiated feline leukemia virus (UV-FeLV) and the retroviral envelope protein p15E of FeLV are immunosuppressive (Stiff and Olsen, 1983; Copelan et al., 1983; Olsen et al., 1983). Their studies demonstrated that IL-2 production by activated T cells was diminished by more than 90% and T-cell proliferation in response to IL-1 was decreased by more than 50% in the presence of UV-FeLV. Dr. Olsen and colleagues have determined that the FeLV immunosuppressant protein p15E markedly impairs the proliferative response of human peripheral blood mononuclear cells to Con A, does not interfere with monocyte helper cell function, and inhibits IL-1 stimulated proliferation of activated T cells secondary to impaired IL-2 production and decreased IL-2 response of T cells. The antiproliferative effect of FeLV is mediated by its p15E protein.

Much of our current understanding of the immunologic defect in AIDS is based on studies of the normal immune system and changes either due to or causative of various disease states, including cancer and immunodeficiency diseases. The ability to rapidly identify a derangement in subsets of lymphocytes of AIDS patients stems from basic studies of functional and phenotypic properties of these lymphocyte subsets. The development of monoclonal antibodies, in conjunction with flow cytometry, has greatly facilitated research in this area; in particular, the production of monoclonal antibodies to human T-cell differentiation antigens has enhanced the study of functional subpopulations of T cells. Monoclonal antibody OKT4 identifies an antigen present on a subset of helper-inducer T cells (Reinherz et al., 1979) and monoclonal antibody OKT8 identifies an antigen present on the cytotoxic-suppressor subset (Reinherz et al., 1980a,b; CA 25369). The OKT4⁺, OKT8⁺ populations are mutually exclusive and together define 80% to 90% of the human peripheral blood T-cell population. The reversal of the normal OKT4:OKT8 ratio (2:1) which is important in the diagnosis of AIDS is also seen in other disease states, and has recently been reported by John Hansen, E. Donnal Thomas, and colleagues (CA 29548) to be reversed in patients following bone marrow transplants for the treatment of acute leukemia or severe aplastic anemia. Both the relative and absolute number of OKT4⁺ cells have been reported to be severely and persistently depleted for up to 2.7 years post-transplant, during which time these patients are susceptible to opportunistic infection (Atkinson et al., 1982). The development of these antibodies is continuing at a rapid pace, and the status of this field has been recently reviewed (Hansen and Martin, 1982, CA 29548; Fox et al., 1982; Fox and Adamson 1983; Fox et al., 1983, CA 28746). It should be noted, however, that surface phenotype does not necessarily correlate with functional immune status and that the subsets of T lymphocytes identified by these monoclonal antibodies are not homogeneous.

To understand further the nature of the immune defect in AIDS and other immune deficiency states, it is necessary to look at the functional reactivity and interactions of the various components of the immune system. The immune system is composed of a network of regulatory circuits and depends on self recognition for cellular communication and for the cooperative events that enable this system to function effectively. The Ia antigens, products of the immune response genes, are

an important set of self determinants recognized by the immune system. Ia antigens are expressed predominantly on non-T cells and can stimulate T cells to differentiate into functional helper and suppressor cells and to produce various factors including interleukin 2 (IL-2, T cell growth factor) which interacts with other T cells to generate various effector T cells. Failure of T cells to recognize Ia cell surface determinants could result in disruption of normal T-cell differentiation pathways leading to various immunodeficiency states. The autologous mixed lymphocyte reaction (AMLR) is a well described phenomenon in which T cells proliferate upon culture with syngeneic or autologous non-T cells. It has been postulated that the AMLR may represent an in vitro manifestation of an immunoregulatory mechanism by which B lymphocyte function is controlled. In the classical AMLR, T cells respond to autologous non-T stimulator cells and it has been shown that this reaction generates both helper and suppressor T cell activity.

Observations of decreased or lack of AMLR in several diseases characterized by autoantibody production--including systemic lupus erythematosus (SLE), chronic lymphocytic leukemia (CLL), rheumatoid arthritis and idiopathic thrombocytopenic purpura--has led to the hypothesis that decreased AMLR results in reduced suppressor cell activation which contributes to the production of autoantibodies. These findings support the contention that the breakdown of autoimmune regulation could plan an important role in the oncogenic process of certain lymphoproliferative and autoimmune diseases. Basic studies such as these may shed light on the curious finding in AIDS patients of decreased cellular immunity accompanied by elevated levels of immunoglobulin.

Howard Ozer and colleagues (CA 27691) have recently reported a complete lack of AMLR between responding T cells or T cell subsets and stimulator leukemic B cells or monocytes in patients with CLL, regardless of disease status, stage, phenotype or karyotype of the disease. The stimulating capacity of CLL B cells and monocytes was significantly depressed and the responding capacity of CLL T cells was also lower than that of normal T cells. Although the depressed AMLR described in this study might be explained on the basis of these defects, these speculations do not adequately account for the complete lack of AMLR in these patients. Dr. Ozer and colleagues observed that normal T gamma cells do not proliferate in response to autologous B cells, while the T non-gamma subset (containing both the helper and radiosensitive mitogen-inducible suppressor subsets) do respond to autologous B cells. However, neither the T gamma subset nor the normally responsive T non-gamma subset from these CLL patients will proliferate in response to autologous leukemic B cells. These observations indicate the absence or dysfunction of autoreactive T cells within the T non-gamma population which may account for the lack of AMLR in patients with CLL (Han et al., 1982).

Edgar Engleman and colleagues (CA 24607) have shown that the induction of immunoglobulin (Ig) synthesis in the AMLR has an absolute requirement for helper/inducer (Leu-3⁺) T cells, whereas an excess of suppressor/cytotoxic (Leu-2⁺) cells suppresses the response. To assess the immunoregulatory potential of T cells activated in the AMLR, T cells were cultured with autologous non-T cells for eight days, after which the activated T cells were fractionated into subsets with monoclonal antibodies to T cell markers and HLA-DR antigen. Each population was co-cultured with fresh T and non-T cells and, on the eighth day of culture, Ig-secreting cells were measured in a reverse hemolytic plaque assay. The results showed that activated Leu-2⁺DR⁺ T cells (but neither Leu-2⁺DR⁻ nor Leu-3⁺ T cells) were at least fifty times more potent as suppressors of IgM and IgG synthesis

than fresh Leu-2⁺ cells alone. The activation of this Leu-2⁺DR⁺ subpopulation required Leu-3⁺ cells in the primary culture. Furthermore, in the absence of Leu-2⁺ cells in the second culture, no suppression was observed, suggesting that Leu-2⁺DR⁺ cells amplify or induce the suppressor effect for the fresh Leu-2⁺ cells (Gatenby et al., 1982a,b). These studies indicate the existence of functionally distinct subsets within the suppressor lineage (Leu-2), but it is not clear whether these subsets derived from a single resting cell type or from phenotypically distinct resting cells. In an attempt to determine the heterogeneity of resting cells within these lineages, new monoclonal antibodies are being developed.

Marc Weksler and colleagues (CA 26344) have found that T cells which respond to autologous non-T cells are distinct to a considerable extent from those responding to allogeneic non-T cells (Kozak et al., 1982). T cells activated in the AMLR lyse a wide variety of target cells including autologous and allogeneic non-T cells, mitogen blasts and natural killer (NK)-susceptible cell lines devoid of HLA determinants. Autoactivation is required to generate these killer cells, as neither fresh T cells nor T cells cultured alone for seven days are capable of lysing any target cells. The data suggest that two distinct populations of killer cells are activated during the AMLR: one which is OKT8⁺ and lyses NK-resistant mitogen blasts, and a second which is OKM1⁺ and lyses the NK-susceptible myeloid line K562. Dr. Weksler and colleagues have also found that DR⁺ T cell lines established from a classical AMLR (T:non-T) and maintained in IL-2 can stimulate autologous T cell proliferation. This (T:T) AMLR was similar to the (T:non-T) AMLR in magnitude and kinetics of the response. The data indicate that the AMLR includes two autologous cell interactions: (1) initially, non-T cells stimulate autologous OKT4⁺ cell proliferation, and (2) OKT4⁺ cells activated in the AMLR acquired DR determinants and stimulate OKT8⁺ cell proliferation. These cells may form a negative feedback loop which down-regulates the AMLR (Tomonari et al., 1982; Moody et al., 1983a; Hausman et al., 1983). Dr. Weksler and colleagues are also studying the syngeneic MLR (SMLR) in mice (CA 13339) and have determined that this response is not demonstrable in Balb/c mice less than three weeks old. The SMLR attains an adult level of activity at four weeks of age and declines with age in this strain of mice. The decline was first documented at twelve months of age, when non-T spleen cells were less able to stimulate young adult T cells than were non-T cells from two to three month-old mice. Splenic T cells from twelve month-old mice were as responsive as splenic T cells from two to three month-old mice. By twenty-four months of age, mice had no significant SMLR activity. Splenic T cells from twenty-four month-old mice did not respond and splenic non-T cells did not stimulate SMLR when cultured with cells from young adult mice. Suppressor cells were demonstrated in spleen cell preparations from twenty-four month-old mice and may explain or contribute to the impaired SMLR in these animals (Gutowski and Weksler, 1982a,b; Moody et al., 1983b).

J. Bruce Smith and colleagues (CA 33556) have shown that the helper cells generated in AMLR mediate this helper activity via a non-IL-2 lymphokine produced by Lyt-1⁺ T cells and that this lymphokine mediates generation of cytotoxic T lymphocytes (CTL) from inactive precursors. Such CTL are antigen-specific and H-2-restricted with respect to target cells. They have also shown that NZB mice, known to be deficient in the AMLR after six to eight weeks of age, are able to produce the AMLR helper factor but lack the subset of T cells able to respond to it. Their studies also suggest that NZB mice of eight to twelve weeks of age have decreased AMLR on the basis of "suppression". Removal of Ia⁺ T cells and

supplementation of cultures with IL-2 unmasks a normal precursor frequency of AMLR responder cells in NZB mice in that age range. Thus up to a certain age--about three months--the AMLR defect in NZB mice is reversible (Bocchieri and Smith, 1982; Smith et al., 1983; Bocchieri et al., 1983). Basic studies such as these continue to contribute to our understanding of the role of the immune system in various disease states.

Molecular Regulation of the Immune System

The normal functioning of the immune system involves the control of its differentiation, the interaction of its cellular components and its response to external stimuli. This immunoregulation involves the expression and interaction of a variety of gene products including immunoglobulins, soluble mediators, cell surface receptors and antigens.

Richard Lynch and colleagues have been studying the regulation of murine myeloma cell growth and differentiation by specific immunoregulatory effectors (CA 32275, CA 32277). They have shown that mice that were immunized with a purified myeloma protein developed idiotype-specific suppressor T cells. These mice generate idiotype-specific antibodies and idiotype-specific transplantation resistance to challenge with lethal doses of myeloma cells. They have additionally shown (Milburn and Lynch, 1982) that this idiotype-specific suppressor T cell selectively inhibits the synthesis and secretion of myeloma protein without interfering with the synthesis of other proteins by the same cells. This suppressive effect is caused by a diffusible product, released by T cells, which is capable of turning off secretion by an actively secreting cell. The suppressor T cell that is generated by these immunized mice is stimulated to produce this diffusible suppressor factor through its ability to recognize a specific segment (idiotope) of the protein molecule. Dr. Lynch and colleagues (Milburn et al., 1983) have additionally shown that the suppression of the synthesis of this myeloma protein is due to the inhibition of the expression of a messenger RNA for a specific portion of the protein molecule. This group has also been studying the effect of anti-idiotypic antibodies on the growth of myeloma cells in mice (Milburn and Lynch 1983). These antibodies do not influence growth, viability or secretion of myeloma protein by these cells but do affect the presence of idiotype on the cell surface. The idiotype/anti-idiotypic form complexes which are attached to vesicles and are shed from the cell surface. The immunoglobulin idiotype can again be found at the cell surface after the depletion of the anti-idiotypic antibodies. In other experiments, Dr. Lynch and colleagues have studied the control of the synthesis of various immunoglobulins by T suppressor cells. They have determined that T suppressor cells with specificity for certain immunoglobulins can be induced *in vivo* and *in vitro* using the appropriate immunoglobulin isotype. Thus, the immunization with IgA myeloma protein can induce the production of a population of T cells which specifically suppresses the synthesis of IgA through the induction of the synthesis of an Fc receptor on the surface of the T cell. Additionally, it has been demonstrated that the IgA surface receptor on myeloma cells can be shed and is capable of specifically suppressing the secretion of myeloma proteins (Hoover et al., 1981; Hoover and Lynch, 1983). These studies are important because they are defining in a clear and precise manner those events that occur during the regulation of the secretion of a specific immunoglobulin.

Bruce Devens (CA 29752) has been evaluating the effect of tumor promoters on the immune system. The tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA) has been studied for its in vitro effects on lymphocyte function (Devens et al., 1982). Using an in vitro allogeneic sensitization system, TPA suppressed this sensitization during the first two days of culture but not thereafter. It appears that TPA is capable of inducing an effect upon undifferentiated cells of the immune system whereas fully differentiated effector cells are not affected. This study is particularly interesting because it is attempting to identify those specific immunological responses which result in the development of a tumor.

Both macrophages and lymphocytes play a major role in the defense by the body to tumor cells. Carl Nathan and colleagues (CA 22090) have been studying the anti-tumor action of phagocytes and lymphocytes. Certain forms of reactive oxygen may play an important role in the antitumor action of phagocytic cells (macrophages, monocytes). This group found that each of eleven murine tumors tested produced a factor that suppressed the ability of macrophages to release reactive oxygen intermediates (H_2O_2 or O_2^-) in response to the presence of phorbol myristate acetate or zymosan (Szuro-Sudol and Nathan, 1982). Four of seven normal cell types produced similar activity although this activity was weaker and could be more rapidly reversed. This factor (1) suppressed the release of reactive oxygen intermediates, (2) had no effect on rates of phagocytosis, synthesis of protein or secretion of various macrophage-associated metabolites, and (3) had an enhancing effect on macrophage spreading and adherence. Thus the factor secreted by these tumor cells appears to selectively deactivate oxidative metabolism with a diminished release of these reactive oxygen intermediates. Functionally, these suppressed macrophages have a reduced ability to kill intracellular pathogens. Whereas tumor cells could be induced to secrete a mediator which depressed the production of reactive oxygen intermediates by phagocytes, human monocytes can also be stimulated by lymphokines to secrete these reactive oxygen intermediates by lymphokines (Nakagawara et al., 1982). Supernatants from mitogen or antigen stimulated human blood mononuclear cells were capable of enhancing the capacity of human monocytes to release reactive oxygen intermediates in response to phorbol myristate acetate or zymosan. Since the function of several catabolic enzymes were not affected by these lymphokine-containing supernatants, the greater release of H_2O_2 was due to its increased synthesis rather than to a decreased catabolism. These studies strongly suggest that the mechanisms whereby phagocytes kill tumor cells can be regulated by soluble mediators. It has also been demonstrated that oxygen plays a role in T-cell mediated cytotoxicity. There has been some controversy over the specific role that oxygen plays in this T-cell function. Dr. Nathan and his group have conducted experiments which indicate that mitochondrial respiration, secretion of reactive oxygen intermediates, and arachidonic acid oxidation do not appear to be involved (Nathan et al., 1982). Thus, although oxygen is involved in cytotoxicity by T cells its role remains to be determined.

Dolph Adams and colleagues have also been studying the mechanisms of immune lysis of tumor cells either by macrophages or lymphocytes (CA 16784, CA 29589). The most probable first event in the lysis of tumor cells by macrophages is the binding of the macrophage to the tumor cell. Research by this group has indicated that there is a high level selective binding between activated macrophages and tumor cells, and there is some evidence that suggests that the specific binding of tumor cell and macrophage is mediated by a receptor on the surface of the macrophage. It is also likely that certain lymphokines are involved in the

specific attachment of the tumor cell to the macrophage receptor (Somers et al., 1983). Additional evidence has been generated by this group that a cytolytic protease is involved in the lysis of tumor cells by macrophages. Evidence for this involvement has been strengthened by the finding that mice whose lymphocytes are unable to complete cytolysis cannot secrete cytolytic protease in response to endotoxin. When macrophages from these mice are induced to release cytolytic protease, they are also capable of lysis (Johnson et al., 1982). The signals that induce the release of cytolytic protease by macrophages are currently being investigated, and it appears that lymphokines are involved.

Robert Schreiber (CA 34120) and Stephen Russell (CA 31199) also have been studying the molecular regulation of macrophage cytotoxic activity and have produced a murine T-cell hybridoma by the fusion of alloantigen activated T cells with a T-cell hybridoma. This hybrid, upon stimulation by mitogens, produces a lymphokine which is capable of inducing tumoricidal activity by macrophages. Evidence produced by Dr. Schreiber and colleagues have indicated that this lymphokine is indistinguishable from macrophage activating factor (MAF) (Schreiber et al., 1982). They have generated a significant amount of evidence, both molecular and biologic, that indicates that MAF produced by a clone of this hybridoma is a form of gamma interferon. Additionally, murine gamma interferon produced by recombinant DNA technology was found to have MAF activity which was quantitatively identical to that produced by the T-cell hybridoma (Schreiber et al., 1983; Pace et al., 1983). Thus, gamma interferon can act as a macrophage activating factor. Dr. Schreiber notes that these results are of particular interest in the light of ongoing clinical trials of interferon.

Janet Plate (CA 25612) and her colleagues have been studying the regulatory mechanisms involved in the development of cytolytic T cells. They have been able to identify the presence of specific helper factors involved in the in vivo generation of cytolytic T lymphocytes in a murine system and have genetically mapped the factor specificity to the H-2D region (Plate et al., 1982). The recipients of allogeneic skin transplants generated T cells that produced a soluble factor capable of interacting with T cells to generate specific T-cell-mediated cytolysis. Dr. Plate has hybridized the T cells from these mice and produced T-cell hybridomas that secrete helper activity in vitro. Preliminary data suggest that the soluble factor may impart specificity to T-cell-mediated killing.

Kendall Smith (CA 17643) is also studying the regulation and control of T-cell proliferation and differentiation. During this current year he has made a significant technical advance in the purification of T cell growth factor (TCGF). This growth factor has been important in the technical accomplishment of maintaining the growth of T cells in vitro and is apparently involved in the regulation and differentiation of T cells in vivo. Dr. Smith has purified TCGF from conditioned medium from a cultured leukemic T-cell line, determined its molecular weight (15,500 D) and the first 20 N-terminal amino acids have been provisionally determined (Robb and Smith 1981; Smith, 1983).

It has been demonstrated by numerous investigators over the past several years that T cells produce soluble factors that are involved in the regulation of B-cell function, macrophage function and the function of other T lymphocytes as well as NK cells. Richard Weisbart (CA 30280) has recently identified a new

factor generated by T lymphocytes which inhibits the migration of neutrophils. This neutrophil migration inhibition factor (NIF-T) is produced by peripheral blood lymphocytes in response to mitogens and spontaneously by a T lymphoblast cell line derived from a patient with a T-cell variant of hairy cell leukemia. NIF-T activity can be removed by normal and leukemic human peripheral blood neutrophils, cells from patients with acute and chronic myelocytic leukemia and one promyeloblast cell line (HL-60) (Weisbart, 1982). These data suggest that human neutrophils and neutrophil precursors express specific binding sites for NIF-T. These studies are important because they identify yet another T-cell soluble mediator that plays a role in the regulation of the immune response.

Human Tumor-Associated Antigens

The Immunology Program supports a number of laboratories which are identifying, isolating and characterizing tumor-associated antigens (TAA's). Some of these studies also include attempts to elucidate the mechanisms of turnover of cell surface molecules, their shedding and degradation. As the structural and functional nature of these molecules is understood, this research can be expected to form the basis for improved identification and/or eradication of tumor cells in vivo and in vitro. Already a number of clinical applications have resulted.

The majority of human TAA studies in the Immunology Program utilize the melanoma system. Melanoma associated antigens (MAA's) are the most extensively characterized of TAA's. A large body of data was generated by the exchange of monoclonal antibodies to MAA's among ten laboratories participating in workshops sponsored by the Immunology Program in the past two years. A number of common antigenic determinants were isolated and partially characterized by these reagents. Details of these studies have been published by the participating laboratories in one volume (Steplewski, 1982) with a summary elsewhere (Reisfeld, 1982). The laboratories are those of Jean-Claude Bystryn (CA 13844), Soldano Ferrone (CA 32609, CA 32619), I. and K.E. Hellstrom (CA 19148, CA 19149, CA 27841, CA 34777), Judith Johnson, Hilary Koprowski (CA 25874), Kenneth Lloyd (CA 21445), Jean-Pierre Mach, Donald Morton, Ralph Reisfeld (CA 28420), and H.F. Seigler. The collaborations stimulated by these workshops continue.

Some accomplishments of the individual laboratories listed above deserve attention. Joseph Brown, in collaboration with I. and K.E. Hellstrom and with William Dreyer (CA 29909), has made one of the first determinations of an amino acid sequence for a TAA as well as obtaining insight into its function. This group has characterized p97 as a cell-surface glycoprotein, molecular weight (M.W.) 97 kilodaltons, having a sequence homologous to the N-terminal sequences of transferrin and lactotransferrin. This macromolecule is seen in most human melanomas with trace quantities in some normal tissues. The antigen is homologous to transferrin and lactotransferrin not only in structure but function, in that it binds iron (Brown et al., 1982). However, p97 apparently is an integral part of the melanoma cell membrane rather than being found in secretions, as are lactotransferrin and transferrin. A possible function of p97 on the cell surface is translocation of iron. Some of the same workers have also determined that the p97 gene is localized on chromosome 3, as are the genes for the transferrin receptor, and possibly for transferrin itself (Plowman et al., 1983).

Michele Pellegrino (CA 32635) and Soldano Ferrone, with other workers, have used monoclonal antibodies to various MAA's to examine tissue distribution and molecular profile of these antigens. One antibody (465.12S) has identified what is apparently the first cytoplasmic MAA to be reported (Natali et al., 1982). This antigen is protein in nature and is composed of four glycopeptides with molecular weights of 25, 70, 75 and 94 kilodaltons. It is found in cultured carcinoma and melanoma cells as well as some normal tissue but is not detectable on melanocytes. Because it is apparently expressed, or increases in expression, upon malignant transformation, it may have future use in monitoring such changes in cells. This group has also demonstrated the antigenic heterogeneity of primary and metastatic melanoma lesions in humans using a battery of monoclonal antibodies to HLA-A,-B, β_2 -microglobulin, Ia antigens, and four MAA (Natali et al., 1983a). Despite apparent morphological homogeneity of primary/metastatic lesions from each individual patient, marked antigenic heterogeneity was observed among different specimens from the same patient. This difference was less noticeable when both primary and metastatic lesions were excised simultaneously. Similar heterogeneity has been found for MAA expression in cultured human melanoma cell lines (Burchiel et al., 1982), as well as in surgically removed primary and autologous metastatic breast carcinoma cells (Natali et al., 1983b). The implication is that a battery of monoclonals would be more effective than a single antibody for either diagnostic imaging or immunotherapeutic applications.

Ralph Reisfeld's laboratory has done extensive studies with monoclonal 9.2.27 which identifies an antigenic complex composed of a 250-kilodalton glycoprotein associated with a proteoglycan having a M.W. of greater than 400 kilodaltons. The antibody reacts only with melanoma cell lines, freshly excised melanoma specimens, and a neuroblastoma cell line. Their data suggest the tumor cell may be expressing unique or modified gene products which could account for changes in the proteoglycan makeup of membranes and extracellular matrices of tumor cells (Bumol and Reisfeld, 1982). Using 9.2.27 alone or coupled with diphtheria toxin A chain, Reisfeld's group has shown suppression of melanoma tumor growth in nude mice (Bumol et al., 1983). While the immunotherapy did not eradicate melanoma per se, the data reinforce the idea that the nature of a target antigen may have substantial impact on control of tumor growth. In collaboration with the National Cancer Institute, Phase I clinical trials have been initiated for Stage IV melanoma patients, based in part on these data.

Another investigation with immunotherapeutic promise arises from studies on MAA's using xenogenic antisera in Jean-Claude Bystryń's laboratory. This group has concentrated and highly purified macromolecules shed by cultured melanoma cells (Heaney-Kieras and Bystryń, 1982) and done extensive studies on the degradation and autocatabolism of tumor-associated antigens shed *in vitro* (Bystryń and Perlstein, 1982; Boctor and Bystryń, 1982). Their data suggest that one pathway for the turnover of surface antigens is shedding and autocatabolism by the releasing cells. The melanoma cells they studied were apparently defective in the extent to which they could catabolize their MAA's, suggesting that *in vivo* there may be a selective local accumulation of these antigens near the tumor. Since the process of release and degradation of TAA's would partially control the concentration of soluble antigens in body fluids, this may have an impact on the ability of tumor cells to escape host immunosurveillance. The shed MAA's are being used for preparation of a polyvalent human MAA vaccine with plans being made to initiate Phase I clinical trials.

A number of studies utilizing TAA's other than melanoma show promise. Kwong-Yok Tsang's laboratory (CA 29377) has succeeded in adapting two osteosarcoma cell lines to serum-free medium. Optimum conditions for synthesis of osteosarcoma-associated antigens have been defined and antigens have been detected both on cell membranes and in culture medium (Tsang et al., 1983). Serum-free conditions have the advantage of eliminating cross-contamination of TAA preparations with serum proteins, as well as avoiding potential TAA alteration via the methods normally employed for separating out TAA's contaminated in such a way. TAA purification and characterization procedures are in progress.

Kenneth Lloyd's laboratory (CA 21445) has utilized monoclonal antibodies to identify cell surface antigens on cultured human astrocytomas and established the preferential expression of some of these determinants on tumors of neuroectodermal origin (Cairncross et al., 1982). Further, they have been able to divide the cultured astrocytomas into subsets, although the functional significance of these phenotypic differences remains to be established. None of the cell surface determinants detected in these studies was present only on tumor cells; however, two determinants found on astrocytoma cells could not be detected in normal brain suggesting they were potential tumor-associated antigens. More sensitive and extensive followup studies are indicated.

Robert Seeger's (CA 22794) laboratory has developed a monoclonal antibody Ab 459 which apparently reacts with an onco-neural antigenic determinant (Seeger et al., 1982). Ab 459 fixes complement and binds to neuroblastoma lines but not leukemia cells or normal hematopoietic elements. Studies employing Ab 459 plus human complement, incubated with cell lines or patient cells, demonstrated significant killing of neuroblastoma cells (65-90%) but indicated that any immunotherapeutic regimen using this antibody, e.g. treatment of autologous bone marrow before transplantation, would need to include other antibodies as well to achieve 100% cytotoxicity of tumor cells (Casper et al., 1983).

Molecular Immunogenetics

The development over the past several years of the capability to manipulate genetic material has had a vast impact upon biological research. The ability to clone genes, insert these genes into different cells and to assess the function of specific genes will continue to advance our knowledge of how living systems function. The following are examples of the usefulness of this technology to immunology and the understanding of the process of oncogenesis.

Jerry Adams and his colleagues (CA 12421) have been studying the structure of immunoglobulin messenger RNA and genes for the past several years. Because of the pivotal effect of T lymphocytes on the regulation and function of the immune system, many laboratories are pursuing the identification and isolation of the T cell receptor(s). Since serologic evidence has implicated the products of the immunoglobulin V_H genes as part of the T cell receptor, Dr. Adams' group has cloned these V_H genes to look for the expression of V_H-bearing mRNA molecules and T cells, T-cell lines and T-cell hybridomas. Since no mRNA's were detectable in any T-cell preparation examined, it seems unlikely that the T cells use the V_H repertoire to code for antigen receptors (Kemp et al., 1982). Chromosomal translocations have been observed in transformed cells for many years. It has

recently come to light that these translocations may have great importance to the transformation process. Murine plasmacytoma cells frequently display a specific translocation from chromosome 15 to the end of chromosome 12 where the immunoglobulin heavy chain locus lies. Since it was known that an unknown region of DNA, called LyR for "lymphoma rearranging DNA," had recombined near the alpha heavy chain gene, Dr. Adams conducted experiments to determine whether it was the LyR region that was translocated. Using probes developed from clones of the LyR region to search for rearrangement in transcription in several murine tumor lines, it was determined that this LyR region was rearranged in 90% of the murine plasmacytomas studied but was absent in normal B lymphoid cells. These results suggested that the LyR region might function in the development of murine lymphomas (Adams et al., 1982). Dr. Adams has determined the chromosome of origin of the non-immunoglobulin DNA which recombined in plasmacytoma cells. The DNA segregated with chromosome 15 in all plasmacytoma cell lines tested. Other data assigned it to the distal two-thirds of that chromosome (Cory et al., 1982). This finding, together with those described above, suggests that translocation activates a gene involved in plasmacytoma oncogenesis. Moreover, rearrangement within the same DNA segment of chromosome 15 in certain T lymphomas implicates the same gene in the oncogenesis of some T lymphomas. In the same murine plasmacytoma system, Dr. Adams and his colleagues determined that the LyR DNA, which is translocated from mouse chromosome 15 to the immunoglobulin heavy chain locus, bears the cellular gene (c-myc) which is homologous to the oncogene (v-myc) of avian retrovirus MC29. In these plasmacytomas, chromosome break points fall near or within the 5' exon and apparently disrupt the normal c-myc transcriptional unit since plasmacytoma c-myc mRNA's differ from the mRNA in cell lines without c-myc rearrangement. Consequently, the translocated gene presumably has lost its 5' regulatory sequences and may well encode an altered myc polypeptide (Adams et al., 1983). Dr. Adams proposes that altered expression of the c-myc gene, which is induced by translocation to an immunoglobulin locus, is a critical oncogenic event for these B lymphoid tumors. Two events may be required for oncogenic transformation because the plasmacytoma oncogene capable of transforming fibroblasts is not c-myc.

Chromosomal translocations in Burkitt lymphoma were first shown in 1972. However, it is only recently that a biological significance of a specific translocation has been developed. Peter Nowell (CA 15822) and colleagues have been studying the biological effects of this translocation. This group has studied cell hybrids between mouse myeloma cells which do not produce immunoglobulin chains and Burkitt lymphoma cells which express surface IgM and which contain a reciprocal chromosome translocation between chromosomes 8 and 14. The data indicated that in this Burkitt lymphoma, the break in chromosome 14 occurred within the chromosome segment containing V region genes. As a result of the translocation some of these V_H genes became associated with chromosome 8. It is possible that the expression of malignancy in Burkitt lymphoma is related to the immunoglobulin V region translocation which results in the activation of a gene on a long arm of chromosome 8 (Erikson et al., 1982).

Carol Jones (CA 18734) has been using somatic hybrids of human and Chinese hamster cells in her analysis of the association of certain T-cell receptors and specific human chromosomes. She has identified that the human transferrin receptor, which is an integral membrane glycoprotein used for iron transport, maps to chromosome 3 region 3q(22-ter) (Miller et al., 1983). Using a similar system, Dr. Jones was able to assign the structural gene for human ferritin to chromosome

19 (Casky et al., 1983). Dr. Jones notes that this association of ferritin with chromosome 19 indicates that the defect in the structural gene for human ferritin cannot account for the abnormalities of hemochromatosis, a disease of iron overload which has been linked to human chromosome 6. The assignment of the human transferrin receptor to chromosome 3 has immunologic significance in that this receptor, found on T cells, is probably involved in the induction and/or regulation of T-cell function.

Conference Support

The Immunology Program contributed to the support of the following conferences in FY 1983:

"Gordon Conference on Immunochemistry and Immunobiology"
February 21-25, 1983 California

"Fifth International Congress of Immunology"
August 21-27, 1983 Japan

FISCAL YEAR 1983

IMMUNOLOGY PROGRAM

SUMMARY OF GRANTS BY SUBCATEGORY

(Includes P01, R01, R23, U01, R13 Grants)

Dollars in Thousands

Subcategory	No. of Grants	Total Costs Awarded
Myeloma Proteins	22	\$ 2,766
Cell Surface Antigens	63	7,662
Cell Surface Determinants of Lymphocytes & Macrophages	50	6,277
Humoral Factors Other Than Antibody	34	3,724
Tumor-Related Antibodies	14	1,498
Immunobiology of Sarcomas, Carcinomas & Melanomas	12	1,220
Host/Tumor Immunopathology	8	1,013
Effects of Disease on Immune Function	25	2,560
Immunotherapy: Mechanisms Rather Than Therapeutic Result	16	2,192
Lymphocytes	95	13,170
Monocytes & Macrophages	32	5,541
Malignancies of the Immune System (Lymphoma/Leukemia)	24	2,365
Immune Surveillance	26	2,965
Immunotherapy in Animal Models	10	909
Bone Marrow Transplantation	5	704
Conference Grants	<u>2</u>	<u>20</u>
	438	54,586

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MYELOMA PROTEINS

R01 CA04946 Bosma	Unexpected Mouse Allotypes Institute for Cancer Research
R01 CA08497 Putnam	Abnormal Proteins in Multiple Myeloma Indiana University, Bloomington
R01 CA10056 Solomon	Proteins in Multiple Myeloma and Related Blood Diseases University of Tennessee, Knoxville
R01 CA12421 Adams	Structure of Immunoglobulin Messenger RNAs and Genes Walter and Eliza Hall Inst. of Medical Research
R01 CA13014 Beychok	Studies on Proteins of Plasma Cell Cancers Columbia University
R01 CA16858 Morrison	Genetics and Biochemistry of Myeloma IG Production Columbia University
R01 CA19616 Edmundson	Immunoglobulins in Multiple Myeloma and Amyloidosis University of Utah
R01 CA22105 Tomasi	Murine Immunoglobulins and B Cell Differentiation University of New Mexico, Albuquerque
R01 CA24432 Haber	Sequence, Shape and Specificity of Antibodies Massachusetts General Hospital
P01 CA25319 Beychok	Synthesis of Human Myeloma Variable Domains in E. Coli Columbia University
R01 CA25754 Storb	Control of Immunoglobulin Synthesis University of Washington
R01 CA28871 Green	IG Processing by Lymphocyte Endoplasmic Reticulum St. Louis University
R01 CA29634 Kemp	Immunoglobulin mRNA and Genes in T Cell Tumors Walter and Eliza Hall Inst. of Medical Research
R01 CA29679 Sibley	Genetic Analysis of Membrane Immunoglobulin University of Washington
R01 CA31013 Blattner	Immunoglobulin Genes of Normal and Leukemic Human DNA University of Wisconsin, Madison
R01 CA31683 Milcarek	Immunoglobulin Gene Expression in Myeloma Mutants Columbia University
R01 CA32044 Robinson	Human Monoclonal Antibodies from EBV Transformed Cells Yale University

R01 CA32497 Structure and Genetics of Antibody Variable Regions
 Cannon University of Massachusetts Medical School

R01 CA32582 Studies on Secretory Immunoglobulin
 Lamm Case Western Reserve University

R01 CA34012 Differentiation Defects in Malignancies of the B Cell
 Vogler Vanderbilt University

R01 CA34127 Antibody Diversity: Comparison of Genes and Proteins
 Gearhart Johns Hopkins University

R01 CA34778 Analysis of Nonsmall Cell Lung Carcinoma Antigens
 Walker Scripps Clinic and Research Foundation

CELL SURFACE ANTIGENS

R01 CA12851 Embryonic and Virally Induced Tumor-Cell Membrane Antigens
 Sanders University of Texas Austin

R01 CA13287 Genetic Basis of Antigenic Variation
 Hyman Salk Institute for Biological Studies

R01 CA13844 Isolation of Tumor Antigens of Human Melanoma
 Bystryan New York University

R01 CA18470 Antigenicity and Tumorigenicity of Somatic Cell Hybrids
 Knowles Wistar Institute of Anatomy and Biology

R01 CA18600 Masking of Antigens at Cancer Cell Surfaces
 Codington Massachusetts General Hospital

R01 CA18609 Biological Role of Alloantigens
 Acton University of Alabama in Birmingham

R01 CA19149 Transplantation Antigenicity of Virus Induced Tumors
 Hellstrom Fred Hutchinson Cancer Research Center

R01 CA19224 Relation of Blood Group and Human Tumor Antigen
 Hakomori Fred Hutchinson Cancer Research Center

R01 CA21223 Antitumor Antibodies Generated In Vitro
 Levy Stanford University

R01 CA21445 Antigens of Malignant Melanoma and Other Human Tumors
 Lloyd Sloan Kettering Institute for Cancer Research

R01 CA22540 Nature of T-Specific Human Carcinoma Antigens
 Springer Evanston Hospital

R01 CA22674 Characterization of Fetal Antigens in Tumors
Coggin University of South Alabama

R01 CA22794 Human Neuroblastoma Antigens
Seeger University of California, Los Angeles

R01 CA23568 Immunoresponse to Human Surface Antigens
Croce Wistar Institute of Anatomy and Biology

R01 CA23770 Antigen Induced Lymphoma
Haughton University of North Carolina, Chapel Hill

R01 CA24263 Hybridomas: Production and Genetic Application
Kennett University of Pennsylvania

R01 CA24358 Leukemia Associated Antigens
Billing University of California, Los Angeles

R01 CA24910 Oncofetal Antigens in Embryogenesis and Tumor Growth
Ostrand-Rosenberg University of Maryland, Baltimore County

R01 CA25134 Lymphocyte Surface Glycoconjugates
Poretz Rutgers--The State University of New Brunswick

R01 CA25139 Study of Group 5 Antigens in Hematologic Malignancies
Lum Fred Hutchinson Cancer Research Center

P01 CA25874 Human Melanoma and Tumor Specific Monoclonal Antibodies
Koprowski Wistar Institute of Anatomy and Biology

R01 CA26184 Antigens of Human Ovarian Tumors
Lloyd Sloan Kettering Institute for Cancer Research

R01 CA26321 Cell-Surface Antigens of Murine Tumors
Allison University of Texas System Cancer Center

R01 CA27124 Molecular Approaches to Human Colon Cancer
Kahan University of Texas Health Science Center, Houston

R01 CA27416 Characterization of New Human IA and Leukemia Antigen
Mohanakumar Virginia Commonwealth University

R01 CA27534 Nucleolar Antigens of Human Cancer Cells
Busch Baylor College of Medicine

R01 CA27628 Tumor-Specific and Tumor-Associated Antigens
Milgrom State University of New York at Buffalo

P01 CA28166 Molecular Immunology and Pathobiology of Neoplasia
Edgington Scripps Clinic and Research Foundation

R01 CA28212 Antisera for Human Tumor-Associated Antigens
Minden National Jewish Hospital and Research Center

R01	CA28420	Molecular Profile of Human Melanoma Antigens Reisfeld Scripps Clinic and Research Foundation
R01	CA28461	Cell Surface Antigens of Sarcomas De Leo Sloan Kettering Institute for Cancer Research
R01	CA28564	Human Squamous Cell Carcinoma: Culture and Serology Carey University of Michigan at Ann Arbor
R23	CA29377	Plasma Membrane Associated Human Osteosarcoma Antigens Tsang Medical University of South Carolina
R01	CA29863	Immunochemical Genetics of Murine Alloantigens Michaelson New York University
R01	CA29886	Tumor-Host Associated Immunological Specificities De Witt University of Utah
R01	CA29909	Molecular Characterization of Human Tumor Markers Dreyer California Institute of Technology
R01	CA29989	HLA Alloantigens on Cultured Human Tumor Cell Lines Pollack Sloan Kettering Institute for Cancer Research
R01	CA30209	Immunochemical Studies of Gastrointestinal Cancer Alpert Baylor College of Medicine
R01	CA30266	Membrane Antigen Organization in Tumor Immunity Gooding Emory University
R01	CA30501	Isolation and Characterization of the Common ALL Antigen Mills City of Hope National Medical Center
R01	CA30561	Tumor Associated Antigens of UV-Induced Tumors Spellman University of New Mexico, Albuquerque
R01	CA31378	Immunochemical Studies of Placental Alkaline Phosphatase Fishman La Jolla Cancer Research Foundation
R01	CA31620	Inappropriate H-2 (K/D) and IE/C Antigens on Tumors Bonavida University of California, Los Angeles
R01	CA31740	Organ Specific Antigens of Gastrointestinal Tissues Gold University of Kentucky
R01	CA31828	Immune Response to Syngeneic Leukemic B Cell Antigens Ricardo Wake Forest University
R23	CA32047	Monoclonal Antibodies to Human Tumor-Associated Antigens Glassy University of California
R01	CA32132	Cross-Reacting Antigens on Spermatozoa and Cancer Cells Anderson Dana-Farber Cancer Institute

- ROI CA32578 Characterization of Tumor Antigen on Leukemia Cells
Garver Medical College of Georgia
- ROI CA32609 Immunochemical Characterization of Antigens in Melanoma
Ferrone Columbia University
- ROI CA32632 Complex Carbohydrate Chemistry in Leukocytes
Klock Medical Research Institute
- ROI CA32635 Antigenic Profile of Human Leukemic Cells
Pellegrino Columbia University
- ROI CA32925 Pancreatic Tumor Antigens Defined by Monoclonal Antibody
Quaranta Scripps Clinic and Research Foundation
- ROI CA33693 MHC Coded Alloantigens on Lung Tumors
Martin U.S. Uniformed Services Univ. of Health Sciences
- ROI CA34031 Analysis of Human Prostate Carcinoma Associated Antigens
Ng Columbia University
- ROI CA34042 Membrane Antigens Which Mediate Metastatic Phenotype
Le Grue University of Texas Health Science Center, Houston
- ROI CA34206 Human Leukemia-Associated Antigens
Pesando Fred Hutchinson Cancer Research Center
- ROI CA34342 Selecting Expressed Tumor Immune RNA with Hybridomas
Paque University of Texas
- ROI CA34368 MHC Antigen Expression on Teratocarcinoma Cells
Ostrand-Rosenberg University of Maryland, Baltimore County
- ROI CA34378 Tumor Cytolysis by Mononuclear Leukocytes
Zucker-Franklin New York University
- ROI CA34777 Molecular Studies of Human Melanoma Antigen p97
Brown Fred Hutchinson Cancer Research Center
- ROI CA34913 Genetics of Response to Histocompatibility Antigens
Howard Institute of Animal Physiology
- ROI CA35857 Immune Regulation to Fetal Antigens in Pregnancy-Cancer
Rohrer University of South Alabama

CELL SURFACE DETERMINANTS

- ROI CA04681 Genetic Studies with Mammalian Cells
Herzenberg Stanford University

R01 CA18640 Silvers	Behavior of Weak Transplantation Antigens University of Pennsylvania
R01 CA18659 Gill	Chemical Genetic and Cellular Aspects of Immunogenicity University of Pittsburgh
R01 CA18734 Jones	Immunologic Studies Related to Malignancy University of Colorado Health Sciences Center
R01 CA20473 Boyse	Immunogenetics of the TLA Region of Chromosome 17 Sloan Kettering Institute for Cancer Research
R01 CA20500 Cullen	Structural and Serological Studies on IA Antigens Washington University
P01 CA21112 Osserman	Clinical and Basic Studies of Plasma Cell Dyscrasias Columbia University
R01 CA21651 Artzt	Teratocarcinoma and Embryonal Tumors: Surface Antigens Sloan Kettering Institute for Cancer Research
R01 CA22131 Boyse	Immunogenetics of Ly Systems Sloan Kettering Institute for Cancer Research
P01 CA22507 Dupont	Immunogenetics of the Major Histocompatibility Complex Sloan Kettering Institute for Cancer Research
R01 CA23027 Flaherty	Immunogenetic Mapping of the Cell Surface New York State Department of Health
R01 CA23469 Yang	Cells Involved in Spontaneous Regression of Tumors University of Connecticut, Storrs
R01 CA24067 Anderson	FC Receptor Structure and Function University of Rochester
R01 CA24433 Sears	Antigen Recognition by Cytotoxic Killer Cells University of California, Santa Barbara
R01 CA24437 Esselman	Expression of T Lymphocyte Differentiation Antigens Michigan State University
R01 CA24473 David	Genetics and Functions of (H-2 Linked) I Region Mayo Foundation
R01 CA25038 Cramer	Major Histocompatibility Complex in the Wild Rat University of Pittsburgh
R01 CA25044 Hickman	Surface IgM of Malignant Lymphocytes and Plasma Cells Jewish Hospital of St. Louis
R01 CA25056 Mishell	Immunoregulatory Effects of Bacterial Substances University of California, Berkeley

R01 CA25532	Glycolipids of Murine and Human Lymphocytes	Eunice Kennedy Shriver Center Mental Retardation
	Schwarting	
R01 CA25893	Cell Surface Molecules: Hematopoietic Differentiation	Salk Institute for Biological Studies
	Hyman	
R01 CA26891	Surface Antigens of Hepatocellular Carcinomas	University of Texas System Cancer Center
	Allison	
R01 CA27824	Plasma Membrane Composition and Immune Function	Duke University
	Whisnant	
R01 CA27955	Role of the H-2NB Gene in Hybrid Resistance to P815	Northwestern University
	Williams	
R01 CA28992	Membrane Lectins on Normal and Neoplastic Lymphocytes	Medical University of South Carolina
	Decker	
R01 CA29194	Somatic Cell Genetics of Cell Surface Antigens	Yeshiva University
	Rajan	
R01 CA29548	Differentiation Antigens on Human Lymphocytes	Pacific Northwest Research Foundation
	Hansen	
R01 CA29657	Genetic Control in Leukemogenesis	Weizmann Institute of Science
	Haran-Ghera	
R23 CA29738	Macrophage Membrane and Immunomodulators	University of Southern California
	Mitchell	
R01 CA30147	Genetic Markers, Leukemogenesis and Thymic Function	University of Texas, Austin
	Gottlieb	
R01 CA30654	Regulation of Immune Responses by FC Portion of Antibody	Scripps Clinic and Research Foundation
	Morgan	
R01 CA31555	Structural Studies of IA Alloantigens	Michigan State University
	Silver	
R01 CA31638	Characterization of MHC Restricted Antigen Presentation	Mayo Foundation
	McKean	
R01 CA31798	Murine T Lymphocyte Cell Surface Antigens	Dana-Farber Cancer Institute
	Springer	
R01 CA31799	Chemistry of Tumoricidal Macrophage Surface Antigens	Dana-Farber Cancer Institute
	Springer	
R01 CA32043	T Cell Recognition of Mutant and Tumor Cell MHC Antigens	Scripps Clinic and Research Foundation
	Callahan	
R01 CA32634	Heterogeneity of HLA-A, B Antigens on Tumor Cells	Scripps Clinic and Research Foundation
	Pellegrino	

R01 CA33555 Cell Surface Antigens on Human Macrophages
 Todd Dana-Farber Cancer Institute

R01 CA34077 IL-2 Action on Normal and Malignant Lymphocyte Receptors
 Mendelsohn University of California, San Diego

R01 CA34108 Structures Related to Function on Cytotoxic T Cells
 Kimura University of Florida

R01 CA34110 Functions of Clonally Derived Human Monocytes
 Twomey Baylor College of Medicine

R01 CA34232 Expression of H-2 Antigens on SJL/ Tumors
 Beisel Johns Hopkins University

R01 CA34787 Human Cell Surface Antigens: Transferrin Receptors
 Trowbridge Salk Institute for Biological Studies

R01 CA34965 Polymorphism of the Major Histocompatibility Complex
 Klein Max Planck Institute for Biology

R01 CA35055 QA and TL Antigens Expressions and Function
 Flaherty New York State Department of Health

R01 CA35638 Molecular Pathway of Human T Cell-Mediated Cytotoxicity
 Ware University of California

R23 CA35976 Characterization of the Cytotoxic T Cell Receptor
 Hunter University of Alabama in Birmingham

R23 CA35986 Monoclonal Antibody Analysis of Cloned/Mutant Killers
 Heagy Dana-Farber Cancer Institute

R01 CA36700 Structural Studies of the Products of the H-2 Complex
 Freed National Jewish Hospital and Research Center

HUMORAL FACTORS OTHER THAN ANTIBODY

R01 CA01786 Human Blood and Tissue Proteins
 Deutsch University of Wisconsin, Madison

R01 CA15129 A Serum Immunosuppressive Factor in Cancer
 Oh Boston University

R01 CA15585 A Soluble Mediator of Tumor-Induced Immunosuppression
 Zolla-Pazner New York University

R01 CA17643 Regulation of T Cell Proliferation and Differentiation
 Smith Dartmouth College

R01 CA19148 Lymphocyte Allogeneic Inhibition and Tumor Immunity
Hellstrom Fred Hutchinson Cancer Research Center

R01 CA19529 Cell-Mediated Immunity in Humans: Mechanisms and Uses
Valentine New York University

R01 CA22720 H-2 Complex and Susceptibility to Mammary Tumor Virus
Long Hahnemann Medical Col. and Hosp. of Philadelphia

R01 CA24474 Generation of Cytotoxic T Cells by Helper Factors
Finke Cleveland Clinic Foundation

R01 CA24974 Chemical and Immunological Characteristics of Thymosin
Goldstein George Washington University

R01 CA25035 The Production and Action of Lymphocyte Interferons
Kamin University of California, San Francisco

R01 CA25943 Immunobiochemistry of Macrophage-Derived Factors
Elgert Virginia Polytechnic Inst. and State University

R01 CA26143 Control of Complement-Mediated Tumor Cell Cytolysis
Lint Rush University

R01 CA26504 Regulation of Granulocyte and Macrophage Production
Stanley Yeshiva University

R01 CA27629 "Tumor Immune" RNA: A Biochemical Characterization
Paque Univ. of Texas Health Science Center, San Antonio

R01 CA27903 The Biology of the Antitumor Actions of Interferons
Epstein University of California, San Francisco

R01 CA30515 Immunological Aspects of Retinoids in Human Cancer
Sidell University of California, Los Angeles

R01 CA30651 Monocyte Tissue Factor: In Vivo and In Vitro Modulation
Edwards University of Connecticut Health Center

R23 CA30669 Growth and Differentiation of Mast Cells and T Cells
Yung Sloan Kettering Institute for Cancer Research

R23 CA30894 Binding Studies with Purified Human T Cell Growth Factor
Mier New England Medical Center Hospital

R23 CA30988 Tumor Specific Helper Factor(s)
Mathews Loyola University Medical Center

R01 CA31394 Effect of Interferon Inducers on NK Cell Cytotoxicity
Lotzova University of Texas System Cancer Center

R23 CA32319 Immunologic Control of Tumor Cell Migration
Cohen University of Connecticut Health Center

R01 CA33168 Thymic Peptides, Monoclonal Antibodies and Cancer
Incefy Sloan Kettering Institute for Cancer Research

R01 CA33557 Transplantation Antigen Specific Immunosuppression
Plate Rush-Presbyterian-St. Luke's Medical Center

R01 CA33653 Mechanism of Immune Interferon Synthesis in Thymocytes
Reem New York University Medical Center

R01 CA33956 Physicochemical Studies of Immune Complexes
Colton Massachusetts Institute of Technology

R01 CA33994 Interferon-Induced Immunosuppression and Tumor Rejection
Korngold Wistar Institute

R01 CA34103 Complement and Immune Complexes in Lymphosarcoma
Day Oklahoma Medical Research Foundation

R01 CA34120 Molecular Regulation of Macrophage Cytocidal Activity
Schreiber Scripps Clinic and Research Foundation

R01 CA34121 Effect of Thymosin on Interferon Induction
Kind George Washington University

R01 CA34141 Isolation of Macrophage Agglutination Factor
Godfrey New York Medical College

R01 CA34951 Nerve Growth Factor and Complement Pathway
Boyle University of Florida

R01 CA35968 Production and Purification of Mouse Immune Interferon
Johnson University of Texas Medical Branch, Galveston

R23 CA35975 Biochemistry and Biological Role of Lymphotoxins
Klostergaard University of Texas System Cancer Center

TUMOR RELATED ANTIBODIES

R01 CA15064 Immunochemical Studies on Carcinogenic Mycotoxin
Chu University of Wisconsin, Madison

R01 CA20045 Antibody Mediated Cell-Cell Interactions
Phillips-Quagliata New York University

R01 CA28149 Immunotherapy of a B Cell Leukemia (BCLI)
Vitetta University of Texas Health Science Center, Dallas

R01 CA29876 Human Hybridoma Antibodies in Neoplastic Disease
Kaplan Stanford University

R01 CA29889	Targeting Antibody-Toxin Conjugates to Leukemia Cells
Houston	University of Kansas, Lawrence
R01 CA30313	New Approaches to the Therapy of a B Cell Leukemia
Slavin	Hadassah University Hospital
R01 CA30647	Synthesis of Human Antibodies to Oncofetal Agents
Irie	University of California, Davis
R01 CA30663	Antibody-Directed Tumor Specific Chimeric Toxins
Collier	University of California, Los Angeles
R01 CA32619	Monoclonal Antibodies to Human Melanoma Antigens
Ferrone	Columbia University
R23 CA33545	Macrophage Differentiation Antigens and Heterogeneity
Kamoun	Oregon Health Sciences University
R01 CA34079	Specificity of Monoclonal Antibodies to Human Cancer
Houghton	Sloan Kettering Institute for Cancer Research
R01 CA35525	Molecular Mechanisms of Induced Immune Cytolysis
Vogel	Georgetown University
R23 CA35692	The Mechanism of Immunotoxin Internalization
Leonard	University of California
R23 CA36703	Macrophage Differentiation Antigens and Heterogeneity
Kamoun	University of Pennsylvania

IMMUNOBIOLOGY OF SARCOMAS, CARCINOMAS, AND MELANOMAS

R01 CA12779	Leukocyte Regulatory Mechanisms
Nowell	University of Pennsylvania
R01 CA12796	Immunogenetics of Tumor Related Alloantigens
Briles	Northern Illinois University
R01 CA14462	Properties of Lymphoid Tumor Cells In Vivo and In Vitro
Thorbecke	New York University
R01 CA19753	Mixed Leukocyte Tumor Reaction in Syngeneic Systems
Bonavida	University of California, Los Angeles
R01 CA28060	Tumor Progression and the Immunobiology of Metastasis
Frost	University of California, Irvine
R01 CA28139	Immunobiology of Tumor Metastases
Feldman	Weizmann Institute of Science

R01 CA28311 Immunobiology of Murine Primary Rous Sarcoma
 Haughton University of North Carolina, Chapel Hill

R01 CA29007 Melanoma Surface Antigens and Cytotoxic T Cells
 Oettgen Sloan Kettering Institute for Cancer Research

R01 CA30461 Clonal Analysis of Cellular Immune Response in Melanoma
 Mukherji University of Connecticut Health Center

R23 CA31732 Tumor Cell Resistance to Destruction by Effector Cells
 Cook National Jewish Hospital and Research Center

R01 CA32591 Regulatory Mechanisms of Neoplasia
 Cerny University of Texas Medical Branch, Galveston

R01 CA35187 Teratocarcinoma Tumor Associated Fetal Embryonic
 De Wolf Beth Israel Hospital

P01 CA16835 Monoclonal Gammopathies--Humoral Immune Status
 Kyle Mayo Foundation

R01 CA17800 Tumor Immunology
 Winn Massachusetts General Hospital

R01 CA23679 Cell Mediated Hyperacute Rejection
 Eichwald University of Utah

R23 CA30110 Vascular Damage in Skin Allograft and Tumor Rejection
 Galli Beth Israel Hospital

R01 CA30169 Bone Allografts for Surgical Oncology
 Friedlaender Yale University

R01 CA30196 Immunopathology of X-Linked Lymphoproliferative Syndrome
 Purtilo University of Nebraska Medical Center

R01 CA30565 Growth Factor(s) in Nodular Sclerosing Hodgkin's Disease
 Newcom Oregon Health Sciences University

R01 CA32577 Studies on Tumor Dormancy and Emergence
 Wheelock Hahnemann University

EFFECTS OF DISEASE ON IMMUNE FUNCTION

R01 CA15462 Suppressor Cells in Neonatal Mice
 Argyris Upstate Medical Center

R01 CA17818 Tumor Immunity and Tumor-Host Interactions
 Stutman Sloan Kettering Institute for Cancer Research

R01 CA20543 Rossen	Antigen-Antibody Complexes in Cancer Patients' Sera Baylor College of Medicine
R01 CA21062 Lotzova	NK Cells in Resistance to Marrow Transplantation University of Texas System Cancer Center
R01 CA24429 Winkelstein	Immunosuppressants and Lymphocyte Function Montefiore Hospital
R01 CA24873 Bankhurst	Immunosuppression in Cancer Patients University of New Mexico, Albuquerque
R01 CA25183 Wood	Immunologic Factors in Central Nervous System Tumors Univ. of Kansas Col. of Health Science and Hosp.
R01 CA26169 Bose	Immunosuppression by Avian Acute Leukemia Viruses University of Texas, Austin
R01 CA29200 Guerry	Autologous Immunity to Human Cultured Melanoma University of Pennsylvania
R01 CA29752 Devens	Immune Response Modulation by Tumor Promoter University of California, Riverside
R01 CA29906 Kadish	Mechanisms of Immunoregulation in Human Cancer Yeshiva University
R01 CA30088 Dray	Synergy of Tumor Chemotherapy and Host Immunity University of Illinois at Chicago
R01 CA30187 Bloom	Regulation of Cell-Mediated Cytotoxicity Mechanisms University of California, Los Angeles
R01 CA30457 Koros	Immunoregulation of Human Tumor Growth in Nude Mice University of Pittsburgh
R01 CA30660 Keller	Immunoregulatory Dysfunctions in Non-Hodgkin's Lymphoma Medical College of Wisconsin
R01 CA31226 Meyers	Tolerance and Immunity to Avian RNA Tumor Viruses and Visa Upstate Medical Center
R01 CA31336 Stackpole	Antigen Evasion as a Tumor Escape Mechanism New York Medical College
R01 CA31547 Olsen	Immunosuppressive Properties of Retrovirus Protein Ohio State University
R01 CA31837 Prehn	Mechanisms of Carcinogenesis Institute for Medical Research, Santa Clara County
R01 CA32070 Platsoucas	Cell Interactions in Leukemia Sloan Kettering Institute for Cancer Research

- R01 CA32275 Immunoregulation of Murine Myeloma
Lynch University of Iowa
- R01 CA32630 Relationship of Tumorigenesis and Immune Responsiveness
Johnson Scripps Clinic and Research Foundation
- R23 CA33012 Cellular Interactions in Hemopoiesis
Steinberg Beth Israel Hospital
- R01 CA34098 Immunoregulatory Factors in Head and Neck Cancer
Veltri Biological Corporation of America
- R01 CA34524 Molecular Mechanism of NK-Cell Mediated Tumor Lysis
Podack Scripps Clinic and Research Foundation

IMMUNOTHERAPY--MECHANISM VERSUS THERAPEUTIC RESULT

- R01 CA20484 Specific Adoptive Immunotherapy of AKR Leukemia
Bortin Mount Sinai Medical Center
- R01 CA26738 Cellular Immunity to Tumors
Zarling University of Minnesota of Minneapolis-St. Paul
- R01 CA27625 Hybrid Tumor Cell Immunotherapy
McCune University of Rochester
- R01 CA28441 Extracorporeal Immunoabsorbents in Immunotherapy
Terman Baylor College of Medicine
- R01 CA28941 Resistance and Sensitization--Role of Lymphocyte Subsets
Deeg Fred Hutchinson Cancer Research Center
- R01 CA29039 Highly Selective Antibody-Ricin A Chain Cytotoxins
Raso Dana-Farber Cancer Institute
- R01 CA31787 Irradiation and Marrow Transplantation in Large Animals
Thomas Fred Hutchinson Cancer Research Center
- R01 CA32123 Augmentation of Human Immunity by Cyclophosphamide
Mastrangelo Fox Chase Cancer Center
- R01 CA33060 Analysis of Immune Complexes from Tumor Scans
Jones Sloan Kettering Institute for Cancer Research
- R01 CA33084 Mechanisms of Murine Tumor Eradication by Immunotherapy
Greenberg University of Washington
- R01 CA33387 Passive Immunotherapy of Spontaneous AKR Leukemia
Weinhold Duke University

ROI CA33677	Immunologic Parameters of BCG Induced Tumor Regression
Kleinschuster	Utah State University
ROI CA34060	Elimination of Neuroblasts from Bone Marrow with AB + C
Boyle	University of Florida
ROI CA34587	Mechanism of Action of Thiabendazole (TBZ)
Lundy	University of Connecticut Health Center
ROI CA34751	Treatment of Suppressor Cell Activity in Melanoma
Livingston	Sloan Kettering Institute for Cancer Research
ROI CA35971	Control of Graft-Versus Host Disease
Parkman	Children's Hospital of Los Angeles

LYMPHOCYTES

ROI CA03367	Natural Resistance to Lymphoma and Marrow Transplantation
Trentin	Baylor College of Medicine
POI CA12800	Immune Functions and Cancer
Fahey	University of California, Los Angeles
ROI CA12844	Controls of Proliferation Specific for Leukemias
Nakamura	State University of New York at Buffalo
ROI CA13339	The Syngeneic MLR and Host Defense Against Cancer
Weksler	Cornell University Medical Center
ROI CA13396	Immunogenesis from Bone Marrow Cells
Miller	Michigan State University
ROI CA14049	Cellular Immunity and Regulatory Factors in Cancer
Amos	Duke University
ROI CA14216	Characterization of Lymphoid Populations in Cancer
Gershon	Yale University
ROI CA15334	Cellular Mechanisms in Tumor-Specific Immunity
Smith	University of Florida
POI CA15822	Immunobiology of Normal and Neoplastic Lymphocytes
Wilson	University of Pennsylvania
POI CA16673	Cell Differentiation Studies in Cancer Immunobiology
Cooper	University of Alabama in Birmingham
ROI CA16885	Propagation of Thymus-Derived Lymphocyte Lines
Ruddle	Yale University

R01 CA17034 Immunology of Human Lymphoid Tumors
 Gajl-Peczalska University of Minnesota of Minneapolis-St. Paul

R01 CA17531 Mechanism and Uses of Anti-Ig Immunosuppression
 Manning University of Wisconsin, Madison

R01 CA17673 Regulation of the Humoral Immune Response by B Cells
 Hoffmann Sloan Kettering Institute for Cancer Research

R01 CA17733 Lymphocyte Antigens: Structure, Function and Synthesis
 Trowbridge Salk Institute for Biological Studies

R01 CA19170 Mechanisms of T Cell Mediated Suppression of Tumor Growth
 Bernstein Fred Hutchinson Cancer Research Center

R01 CA19334 Antigen Receptor of Continuous T Killer Cell Line
 Dennert Salk Institute for Biological Studies

R01 CA20531 Genetic Analysis of Normal and Malignant Lymphocytes
 Yunis Dana-Farber Cancer Institute

R01 CA20819 Phagocytic Cells: Regulation, Dysfunction and Disease
 Van Epps University of New Mexico, Albuquerque

R01 CA20823 Lymphocyte Production and Traffic in the Bone Marrow
 Rosse University of Washington

R01 CA22126 Ultraviolet Light Radiation and Immunoregulation
 Daynes University of Utah

R01 CA22241 T Cell Development: Immunogenetics, Defects, Therapy
 Scheid Sloan Kettering Institute for Cancer Research

R01 CA22677 Pathobiology of Myeloma and Anti-Idiotypic Immunity
 Schreiber University of Chicago

R01 CA22786 Receptor Dynamics and Normal/Tumor Cell Function
 Bankert Roswell Park Memorial Institute

R01 CA23262 Terminal Transferase in Normal and Leukemic Lymphoid Cells
 Bollum U.S. Uniformed Services Univ. of Health Sciences

R01 CA23354 Human Natural Killing: Regulation and Recognition
 Koren Duke University

R01 CA24338 Studies of Normal and Neoplastic Lymphocytes
 Fu Rockefeller University

R01 CA24436 Lymphocyte Receptor Function
 Wofsy University of California, Berkeley

R01 CA24442 Chemical Basis for Receptor Recognition of Lysozymes
 Sercarz University of California, Los Angeles

RO1 CA24472	The Development of Thymocytes and Their Progeny
Basch	New York University
RO1 CA24607	Suppressor T Cells of Mixed Leukocyte Reaction in Man
Engleman	Stanford University
RO1 CA25054	Cellular Mechanisms Regulating Antibody Production
Mullen	University of Missouri, Columbia
RO1 CA25253	Immunoregulatory Network Probed by Cell Hybridization
Bankert	Roswell Park Memorial Institute
RO1 CA25416	Immunogenetics of NK-1+ Natural Killer Cells
Koo	Sloan Kettering Institute for Cancer Research
RO1 CA25583	Cell Mediated Immunity in Mammary Tumor Models
Lopez	University of Miami
RO1 CA25612	Immunologic Effects on Tumor Growth and Rejection
Plate	Rush University
RO1 CA25738	T Cell Differentiation: Molecular Mechanisms
Scheid	Sloan Kettering Institute for Cancer Research
PO1 CA25803	Control of Normal and Abnormal Cell Development
Klinman	Scripps Clinic and Research Foundation
RO1 CA26284	Regulation of Adenosine Deaminase in Human Cells
Daddona	University of Michigan at Ann Arbor
RO1 CA26297	Primary Structure of MHC I Region Associated Antigens
McKean	Mayo Foundation
RO1 CA26695	Antigen-Specific T Cell Clones: Generation and Analysis
Cantor	Dana-Farber Cancer Institute
RO1 CA27691	T Cell Subset Immunoregulation--Myeloma and CL Leukemia
Ozer	Roswell Park Memorial Institute
RO1 CA28533	Mechanisms of Tumor Destruction by Immune Effectors
Russell	Washington University
RO1 CA28708	Immunoregulation of Myeloma Cell Differentiation
Rohrer	University of South Alabama
PO1 CA28900	Control of Antigen-Specific T Cell Responses
Eisen	Massachusetts Institute of Technology
RO1 CA28936	Immunoregulation in Autoimmunity and Malignant Disease
Haynes	Duke University
RO1 CA29282	Prothymocyte Maturation and Function
Waksal	Tufts University

P01 CA29606 Immunoregulation--T Cells and Their Products
Gershon Yale University

R01 CA29635 Analysis of Human T Lymphocyte Subsets Grown In Vitro
Pauly Roswell Park Memorial Institute

R23 CA29803 Cytotoxic Cell Responses to Non-H2 Antigens
Macphail Sloan Kettering Institute for Cancer Research

R23 CA30183 Bone Marrow Cytotoxic Precursor T Cells
Klimpel University of Texas Medical Branch, Galveston

R01 CA30280 T-Lymphocyte Regulated Tumor Cell Killing by Neutrophils
Weisbart University of California, Los Angeles

R01 CA30972 Marrow Prostaglandins and T Cell Differentiation
Bockman Sloan Kettering Institute for Cancer Research

R01 CA31534 Isotype Switching in a Neoplastic B Cell Model, BCL1
Tucker University of Texas Health Science Center, Dallas

R01 CA31564 Role of Glycolipids in Glioma Resistance to Cytolysis
Yates Ohio State University

R23 CA31591 Regulation of Human B Cell Proliferation
Yen University of Iowa

R01 CA31687 Mechanisms of Lymphocyte Colony Formation
Donnenberg Johns Hopkins University

R01 CA31918 Antibody Dependent Cell Cytotoxicity Reaction Mechanism
Fanger Dartmouth College

R01 CA31982 Cytotoxic T Lymphocytes: Mechanisms of Generation
Ballas University of Iowa

R01 CA32018 T Subset Interactions in Specific Tumor Immunotherapy
Perry Emory University

R01 CA32277 FC Receptor-Bearing T Lymphocytes in Murine Myeloma
Lynch University of Iowa

R23 CA32593 Cytotoxic T Lymphocyte Lines to Murine Plasmacytomas
Giorgi Massachusetts General Hospital

R01 CA32685 The Immunobiology of Human Antileukemic Lymphocytes
Sondel University of Wisconsin, Madison

R01 CA32739 Human T Lymphocyte Antigens and Their Genes
Levy Stanford University

R23 CA32757 Mechanisms of Minor-H Antigen GVHD
Hamilton University of Washington

R01	CA32801	Immune Responses to Chemically-Induced Tumors Thorbecke New York University
R01	CA32841	Effector Mechanisms in Rejection of SV40-Induced Tumors Gooding Emory University
R23	CA32969	Functional Studies of Transformed Natural Killer Cells Johnson University of Nebraska Medical Center
R01	CA33104	Somatic Cell Genetic Analysis of T Cell Differentiation Basch New York University
R01	CA33529	Processing of IA Molecules in B Cells and Macrophages Cullen Washington University
R01	CA33556	Autologous Mixed Lymphocyte Interactions Smith Thomas Jefferson University
R01	CA33939	Lymphoid Cell Treatment of Leukemia Furmanski AMC Cancer Research Center and Hospital
R01	CA34105	Immunoregulation: Idiotypic Networks and Clonal Dominance Brown St. Jude Children's Research Hospital
R01	CA34106	Murine T Cell IA Antigens Hayes University of Wisconsin, Madison
R01	CA34107	Mineral Elements in the Generation of Cytotoxic T Cells Flynn Cleveland Clinic Foundation
R01	CA34109	Helper Cells/Factors from Nonresponders Waltenbaugh Northwestern University
R01	CA34112	Molecular Mechanisms in Cellular Immunology Callewaert Oakland University
R01	CA34129	Regulation of Human and Murine Cytolytic T Lymphocytes Burakoff Dana-Farber Cancer Institute
R01	CA34189	Post-Thymic T Cell Lineage Analysis Miller Boston University
R01	CA34546	Studies of Normal and Neoplastic Lymphocytes Fu Oklahoma Medical Research Foundation
R23	CA34670	Role of C-Reactive Protein in the NK Response Baum Univ. of Health Sciences/Chicago Medical School
R01	CA34817	Regulation of Activity in Cloned Anti-Tumor Lymphocytes Russell Washington University
R01	CA34899	In Vitro Analysis of Antibody Regulation in Humans Stevens University of California, Los Angeles

R01 CA34902 Analysis of Neonatal H-2 Tolerance
Streilein University of Texas Health Science Center, Dallas

R01 CA34976 Etiology and Immunological Basis of the AID Syndrome
Valentine New York University

R23 CA35496 Regulatory Mechanisms in Cell-Mediated Immunity
Susskind Virginia Commonwealth University

R01 CA35704 Mechanisms of Antigen Processing of Hemoglobin
Kazim University of New Mexico

R01 CA35730 Requirements for B Cell IA-Alloantigen Presentation
Kubo National Jewish Hospital and Research Center

R01 CA35791 Role of NK Cytotoxic Factor NKCF in NK Cytotoxicity
Bonavida University of California

R01 CA35978 The Role of Gangliosides in Modulation of Mitogenesis
Merritt George Washington University

R01 CA36107 Immune Response to Modified Self and Tumor Antigens
Scott University of Rochester

MONOCYTES AND MACROPHAGES

R01 CA14113 Macrophage Activation for Tumor Cell Cytotoxicity
Shin Johns Hopkins University

P01 CA14723 Study of Experimental Cancer Immunology
Benacerraf Harvard University

R01 CA16784 Tumoricidal Effects of Macrophages: Pathologic Study
Adams Duke University

R01 CA19052 Development and Function of Activated Macrophages
Moore Sloan Kettering Institute for Cancer Research

R01 CA20822 Cell Interaction and the Clotting System
Colvin Massachusetts General Hospital

R01 CA21225 Surface Protein GP160 in Macrophage Activation
Remold-O'Donnell Center for Blood Research

R01 CA22090 Antitumor Action of Phagocytes and Lymphocytes
Nathan Rockefeller University

R01 CA26467 Effector and Suppressor Mechanisms in Tumor Immunity
Stout Brandeis University

R01	CA26846 Musson	Mechanism of Human Monocyte Differentiation National Jewish Hospital and Research Center
R01	CA27523 Evans	Macrophages and Tumor Growth Jackson Laboratory
R01	CA27639 O'Dorisio	Inhibition of Macrophage Tumor Cell Cytotoxicity Ohio State University
R23	CA28935 Cameron	Macrophage Mediated Tumor Cytotoxicity Medical University of South Carolina
R01	CA29266 Weiner	Characterization of Monocyte Subsets in Blood University of Florida
R01	CA29336 Erickson	Macrophage-Mediated Cytotoxicity of Tumor Targets University of California, Davis
P01	CA29589 Adams	Macrophage Activation: Development and Regulation Duke University
P01	CA30198 Silverstein	Human Mononuclear Leukocytes in Cancer Rockefeller University
R23	CA30631 Price	Targets of a Leukosis Virus Infection Trenton State College
R01	CA31199 Russell	Macrophage-Mediated Injury Causing Tumor Regression University of Florida
R01	CA31447 Zwilling	Prostaglandin Control of Macrophage Antitumor Activity Ohio State University
R01	CA32551 Stanley	Hemopoietic Stem Cell Differentiation to Macrophages Yeshiva University
R01	CA32898 Trinchieri	Differentiation and Function of Human Monocytes Wistar Institute of Anatomy and Biology
R23	CA33003 Becker	Characterization of Human Macrophage Heterogeneity University of North Carolina, Chapel Hill
R01	CA33188 Furmanski	Macrophage Control of Normal and Leukemic Erythropoiesis AMC Cancer Research Center and Hospital
R01	CA33225 Pelus	Regulation of Myeloid Progenitor Cell Differentiation Sloan Kettering Institute for Cancer Research
R01	CA33558 Kim	Development and Function of Pulmonary Macrophages Sloan Kettering Institute for Cancer Research
R01	CA33629 Kaplan	Differentiation and Anti-Tumor Activity of Macrophages University of Kentucky

- R01 CA34071 Macrophage Procoagulants
Shands University of Florida
- R23 CA35715 Metabolic Events Related to Macrophage Activation
Klykken University of Mississippi Medical Center
- R01 CA35893 A Mechanism by Which Macrophages Injure Cancer Cells
Granger Duke University
- R01 CA35961 Macrophage Resistance Versus Viruses and Tumors
Morahan Medical College of Pennsylvania
- R23 CA36643 Role of Complement in the Immunopathology of Macrophages
Newman University of North Carolina
- R01 CA36722 Calcium Transport in Activated Macrophages
Gorecka-Tisera University of Pittsburgh

MALIGNANCIES OF THE IMMUNE SYSTEM (LYMPHOMA/LEUKEMIA)

- R01 CA08975 Human Leukemia Associated Antigens
Metzgar Duke University
- R01 CA15472 Immunity and Myeloma Tumors
Eisen Massachusetts Institute of Technology
- R01 CA17276 Membrane Antigens from Normal and Leukemic Lymphocytes
Tanigaki Roswell Park Memorial Institute
- R01 CA20499 Immunobiology of Cutaneous T Cell Lymphomas
Edelson Columbia University
- R01 CA24950 A Thymus Determined Mechanism of Leukemia Resistance
Datta Tufts University
- R01 CA25097 Differentiation of Immune System: Cell Surface Antigens
Kersey University of Minnesota of Minneapolis-St. Paul
- R01 CA25369 Human Leukemia Antigens: Isolation and Characterization
Schlossman Dana-Farber Cancer Institute
- R01 CA25873 Membrane Proteins of Human Leukemias and Lymphomas
Humphreys University of Massachusetts Medical School
- R01 CA26479 Immune Functions of Tumor Cell Variants
Fuji Roswell Park Memorial Institute
- R01 CA29655 Cytogenetic Studies of Human Myeloma
Mackenzie University of California, Davis

R01 CA29964 UNC-CH Immunocytomas
 Haughton University of North Carolina, Chapel Hill

R01 CA31479 Proliferation and Differentiation in Human Lymphoma
 Ford University of Texas System Cancer Center

R01 CA31685 Differentiative Programs of Lymphoid Progenitor Cells
 Lebien University of Minnesota of Minneapolis-St. Paul

R23 CA31888 Monoclonal Antibodies Reactive with Human Leukemia Cells
 Ball Dartmouth College

R01 CA32563 Pathogenesis of Preleukemic Aplastic Anemia
 Hoover Colorado State University

R23 CA32800 Monocytes and the Immunodeficiency of Hodgkin's Disease
 Zamkoff Upstate Medical Center

R01 CA32826 Glycosphingolipids in Oncogenesis and Differentiation
 Macher University of California, San Francisco

R23 CA33127 Regulation of Erythropoiesis in B Lymphocyte Neoplasms
 Mangan Montefiore Hospital

R01 CA34052 T Cell Interactions with Cloned IA+ Accessory Cells
 Kaplan University of Kentucky

R23 CA34313 Antigen Expression on Fetal and Malignant Leukocytes
 Hofman University of Southern California

R01 CA34549 Role of Natural Cytotoxic Cells in Experimental Lymphoma
 Ponzio University of Medicine and Dentistry of New Jersey

R01 CA35207 Lymphoblastoid Receptors for Epstein-Barr Virus
 Fowler University of North Carolina

R23 CA35463 Monoclonal Antibodies Specific for Hairy Cell Leukemia
 Posnett Rockefeller University

R01 CA36040 Defects of AML Leukemia In Replication and Maturation
 Chiao New York Medical College

IMMUNE SURVEILLANCE

R01 CA15988 Immune Surveillance and Cancer
 Stutman Sloan Kettering Institute for Cancer Research

R01 CA19754 Immunoselection and Cancer: A Problem in Evolution
 Cohn Salk Institute for Biological Studies

RO1 CA20408	Immunodeficiency and Tumorigenesis
Shultz	Jackson Laboratory
RO1 CA20816	Pathogenesis of Autoimmunity
Gershwin	University of California, Davis
RO1 CA20833	Cell-Mediated Cytotoxicity in Humans
Trinchieri	Wistar Institute of Anatomy and Biology
RO1 CA22517	Monocyte Function in Neoplasia
Normann	University of Florida
RO1 CA23809	Natural and Tissue-Specific Immunity to Human Neoplasms
Saksela	University of Helsinki
RO1 CA25250	Natural Killer Cells Target Sites, Genetic Control, and Role
Klein	Caroline Institute
RO1 CA25641	Effect of Cancer on Human Monocyte Cytotoxic Mechanisms
Lo Buglio	University of Michigan at Ann Arbor
RO1 CA25917	Cellular and Genetic Aspects of Antitumor Immunity
Daynes	University of Utah
RO1 CA26344	Autologous Lymphocyte Reactions and Immune Surveillance
Weksler	Cornell University Medical Center
RO1 CA26782	Regulation by Natural Killer Cells
Kiessling	Caroline Institute
RO1 CA28231	H-2 Associated Natural Resistance
Carlson	Jackson Laboratory
RO1 CA28834	Basophil/Mast Cell Function in the Control of Cancer
Dvorak	Beth Israel Hospital
RO1 CA29355	T Cell Nonresponsiveness in Gross Virus-Infected Mice
Blank	University of Pennsylvania
RO1 CA29910	Human NK Cells, Interferon(s) and Leukemia/Lymphoma
Pattengale	University of Southern California
RO1 CA30115	Immune Reactivity to Primary Sarcomas in Mice
Babcock	University of Texas Health Science Center, Houston
RO1 CA32553	Specific Anti-Tumor Activity by Armed Lymphoid Cells
Pollack	University of Washington
RO1 CA33858	Cellular Immunity to Endogenous AKR Leukemia Viruses
Green	Fred Hutchinson Cancer Research Center
RO1 CA34199	Genetics and Regulation of Cell Mediated Cytotoxicity
Clark	Genetic Systems Corporation

- R01 CA34461 Regulation of Natural Killer Cells
Welsh University of Massachusetts Medical School
- R01 CA34529 Oxidative Regulation of Human Natural Killer Cells
Seaman University of California, San Francisco
- R01 CA34674 Study of Acquired Immunodeficiency and Kaposi's Sarcoma
Hersh University of Texas System Cancer Center
- R01 CA35979 T Lymphocyte Specific Genes
Storb University of Washington
- R01 CA36033 Regulation of Human Natural Killer Lymphocyte Activity
Kay University of Nebraska Medical Center

IMMUNOTHERAPY IN ANIMAL MODELS

- R01 CA11898 Brain Tumors: Immunological and Biological Studies
Bigner Duke University
- R01 CA16642 Immunological Basis of Tumor Regression
North Trudeau Institute
- R01 CA27794 Mechanisms of Endotoxin-Induced Tumor Regression
North Trudeau Institute
- R01 CA29992 Prevention of Oncogenesis Via Marrow Transplantation
Pierpaoli Foundation for Basic Biomedical Research
- R01 CA30303 Selective Stimulation of Cell Mediated Cancer Immunity
Hunter Emory University
- R01 CA31859 Immunotherapy of Cancer with TCGF-Grown Cytotoxic Cells
Kedar Hebrew University of Jerusalem
- R01 CA32045 Monoclonal Antibody Analysis and Therapy of B 16 Melanoma
Herd Oberlin College
- R23 CA32109 Adsorbed Leukemic Sera Depress Cultured Blast Viability
Miller University of Minnesota of Minneapolis-St. Paul
- R01 CA35299 T Cells and Their Lymphokines in Cancer Immunotherapy
Altman Scripps Clinic and Research Foundation

BONE MARROW TRANSPLANTATION

- R01 CA20044 Transplantation Immunology
Winn Massachusetts General Hospital

- RO1 CA28701 Chronic Graft-Versus-Host Disease in Radiation Chimeras
 Beschorner Johns Hopkins University
- RO1 CA29592 Active Specific Immunotherapy in Man: A Murine Model
 Kahan University of Texas Health Science Center, Houston
- RO1 CA33794 Minor Alloantigens in Clinical Graft-Versus-Host Reaction
 Elkins Children's Hospital of Philadelphia
- RO1 CA33958 Lymphocyte Function in Normal and Chimeric Models
 Sprent University of Pennsylvania

CONTRACT RESEARCH SUMMARY

Title: Resource Bank and Distribution Center for Cell Lines Useful in
Research in Tumor Immunology

Principal Investigator: Dr. Anita C. Weinblatt
Performing Organization: American Type Culture Collection
City and State: Rockville, MD

Contract Number: N01-CB-15533
Starting Date: 9/28/81
Expiration Date: 9/27/86

Goal: To provide an efficient system for the acquisition, cataloging, storage and maintenance of cell lines which are capable of long term growth in vitro and are useful in tumor immunology research. To offer to recipients expert advice on culture and characteristics of all lines shipped.

Approach: The cell lines in the bank are listed in a catalog, which is updated annually. New acquisitions are also announced in quarterly newsletters. The cell lines in the bank include, but are not limited to: B and T cell lines; lines useful in the study of macrophage/monocyte development; myelomas and their variants; cell lines useful in the study of immune effector mechanisms; and hybridomas. Lines are shipped for a fee upon request. These lines are screened for contamination with bacteria, fungi and mycoplasma; detailed characterizations are performed. Relevant lines are actively sought and persons wishing to donate lines are encouraged to contact the principal investigator or the project officer.

Progress: Cell line shipments are averaging approximately one-hundred per month. A large spectrum of hybridomas is offered. These hybridomas secrete monoclonal antibodies with specificities that include: Thy-1.1; Thy 1.2; various antigens on leukocytes, red blood cells, macrophages; brain clathrin. T- and B-lymphocyte antigens including alleles of Lyt-1 and Lyt-2; immunoglobulin fragments; I-A determinants; and sheep red blood cells. Other interesting lines are: HuT 78 (TIB-161), a human cutaneous T cell lymphoma with properties of a mature T cell line; and EL4.IL-2 (TIB-181), a high IL-2 (T-cell growth factor) producer. Another IL-2 producer, HuT 102 (TIB-162), also releases a unique type C retrovirus associated with T-cell lymphomas and will be ready for distribution shortly. YAC-1 (TIB-160) is a lymphoma line, which is often used as a target in NK assays. P388D₁ (TIB-63) secretes IL-1 and is a monocyte/macrophage line that is very popular. Two other high-demand lines are rat-mouse hybridomas M1/42.3.9.8 (TIB-126) and M1/70.15.11/2 (TIB-128). TIB 126 secretes HLK (rat) antibody reactive with H-2 antigen (all haplotypes) and TIB-128 secretes HL (rat) antibodies which react with the murine macrophage-granulocyte specific antigen MAC-1. Consistently requested are the mouse fusion line P3/NS1/1-Ag4-1 (TIB-18) and the non-secreting mouse myeloma S194/5.XX0.BU.1 (TIB-20). Efforts are underway to acquire one or two T-T hybridomas that produce macrophage activating factor (MAF).

Project Officer: Judith M. Whalen
Program: Immunology Section
FY 83 Funds: \$224,181

B

CANCER DIAGNOSIS RESEARCH PROGRAM

DESCRIPTION

The Cancer Diagnosis Research Program emphasizes research in early detection, diagnosis (which includes staging and prognosis), tumor localization, and monitoring the changes during therapy or progression of disease. The program also seeks to apply the knowledge obtained to appropriate populations for clinical evaluation. Projects in these areas are frequently concerned with improvement of existing methodologies as well as the development of new tests and procedures. Many of the projects in the Cancer Diagnosis Research Program have begun in a more basic area such as, Tumor Biology, Tumor Immunology, or General Medical Sciences for instrument development. As a basic concept becomes potentially useful in one of the areas of cancer diagnosis the project may be transferred to the Cancer Diagnosis Research Program. In the earliest stages, diagnostic research is not necessarily site (or even disease) oriented.

The major objective of the program is to recognize or detect cancer at the earliest possible stage to allow appropriate therapy to begin. Early detection and early treatment should improve the chances for the control of cancer, decrease mortality from the disease and increase survival and quality of life of those with cancer. Additionally, early detection is providing greater understanding of the natural history of different types of cancer in the early stages of disease.

Since the techniques of cancer detection and diagnosis are useful for many, or all, types of cancer the divisions of the program are not by cancer type or organ site, but by technical discipline. The Diagnosis Research Program consists of projects in five disciplinary categories: Biochemistry, Immunodiagnosis, Cytology, Pathology, and those projects that are clearly Multi-Disciplinary. Research in diagnostic imaging is managed by the Diagnostic Imaging Research Branch, DCT.

To stimulate research in specific areas, the following program announcements were issued during this reporting period:

1) Development of Myeloma or Human B Cell Lines Suitable for Somatic Cell Hybridization to Produce Human Monoclonal Antibodies.

This announcement is intended to stimulate the development of human cell lines of plasma cell or B lymphocyte origin that are capable of serving as fusion partners for the production of human-human hybridomas synthesizing human monoclonal antibody.

2) Immunohistochemical Classification of Solid Tumors.

The purpose of this announcement is to solicit applications to employ immunohistochemical techniques to examine fixed or frozen tissues from biopsies, surgical specimens and autopsy material to establish retrospective correlation with clinical features which may provide indications for immunochemical markers that can aid in determining prognosis, selection of therapy, detection of early recurrent tumor, etc.

3) Non-Invasive Approach for Detection of Lung Cancer.

This announcement invites grant applications from interested investigators for pilot studies involving the use of gas chromatographic-mass spectrometric techniques for the chemical analysis of the volatile organic components of human expired air in an attempt to identify and quantitate characteristic constituents associated with lung cancer which may have potential for the early diagnosis of this malignancy.

4) Specific Immunoassays for Cancer Associated Isoenzymes.

The objective of this announcement is to encourage submission of grant applications for studies involving the development of sensitive quantitative assays using monoclonal antibodies which could accurately identify and monitor levels of various isoenzymes that have been shown to be quantitatively increased in certain cancers.

In addition to the above program announcements, another announcement entitled "Application of Recombinant DNA Technology to Diagnosis of Cancer" will also be publicized. This RFA is intended to solicit applications to search for novel approaches to diagnosis of cancer exploiting cellular changes at the molecular level employing recent advances in recombinant DNA technology.

The distribution of contracts and grants currently included (FY1983) in the Diagnosis Research Program in the various categories is summarized in the following table. Each category is discussed in the sections following the table.

TABLE 1
 CANCER DIAGNOSIS RESEARCH PROGRAM
 ALL PROJECTS EFFECTIVE DURING FISCAL YEAR 1983

Number	Category	Grants		Contracts	
		Number	Current Funding (in Thousands)	Number	Current Funding (in Thousands)
1	Biochemistry	19	\$ 1,601	0	0
2	Immunodiagnosis	40	4,675	10	\$ 1,086
3	Cytology	24	3,141	0	0
4	Pathology	6	424	0	0
5	Multiple Disciplines	5	270	5	2,534
Totals		94	\$ 10,443	15	\$ 3,620

CANCER DIAGNOSIS RESEARCH PROGRAM

1. BIOCHEMISTRY

Biochemical methods to improve diagnosis and detection of cancer involve the study of a variety of substances such as hormones, enzymes, proteins and metabolic products in the circulation and in other biological fluids, as well as the study of surface characteristics of tumor cells and chemical characterization of tumor cells.

Under hormonal studies, the measurement and mode of action of the multiple forms of human growth hormone are being studied under grant CA-33615. Grant CA-30687, is designed to study and develop an assay for a group of progesterone-dependent proteins synthesized by the human endometrium and obtained from human uterine luminal washes to characterize them and probe their usefulness as discriminants in diagnosis, prognosis and in monitoring response to treatment. Identification, isolation and characterization of the thyroid stimulating factor responsible for thyroid hyperfunction in patients with trophoblastic tumors, especially hydatidiform mole, are being pursued under grant CA-31218. A new grant CA-33207 will establish cultures of human medullary carcinoma of the thyroid and study the molecular forms of calcitonin produced and the regulation of this process. A series of experiments have been proposed in grant CA-29062 to evaluate the clinical use of a material which is cross-reactive to vasoactive intestinal peptide (VIP-CRM) as a biochemical marker to refine the diagnosis of acute and chronic leukemias and to study its role in the function of human lymphocytes. Initial studies are very promising and indicate that VIP-CRM may be an effective means of predicting the onset of blastic crisis in CML and may characterize the blastic transformation as myeloid or lymphoid.

A variety of enzymes are being studied for their correlation with different cancers. Creatine kinase isozyme BB and carcinoembryonic antigen (CEA) are being simultaneously measured in sera and malignant effusions from various cancer types to assess their predictive value in diagnosis and in monitoring of disease response during chemotherapy under grant CA-32585. The biochemical characterization of isozyme 5 of acid phosphatase and its clinical implications in the diagnosis and prognosis of prostatic cancer, of hairy-cell leukemia and bone malignancies are topics of investigation for grant CA-34881. Preliminary studies have clarified the relationship of isozyme-5 to prostatic acid phosphatase. Studies of 5'-nucleotide phosphodiesterase isozymes which have been shown to be elevated in patients with known hepatic metastases from mammary carcinoma and melanoma will be continued under grant CA-25376. Differentiation of lymphocytes by the synthesis of the enzyme marker, terminal deoxynucleotidyl transferase (TdT), is being investigated under grant CA-22599 by determination of the relationship of presence or absence of the enzyme to particular cell sets and to tumors representing those cell sets. The differentiative potential of cells transformed by Abelson Leukemia Virus and chemical carcinogens will be further determined.

Proteins as discriminants of cancer are being investigated under several grants. Computer assisted protein analysis of pancreatic secretions is being probed for diagnostic potential in pancreatitis and pancreatic cancer under grant CA-14380. Intercellular matrix proteins are being extracted from human chondrosarcomas in grant CA-23945 and compared with normal articular cartilage

to evaluate degree of malignancy and possibly grade chondrosarcomas biochemically as well as morphologically. Methods are being developed to determine if plasma levels of these proteins can be used preoperatively in the initial diagnosis of chondrosarcomas and postoperatively to detect recurrences. A new investigator research grant, CA-30667, aims to exploit the differences in lectin binding characteristic of the mucin found in normal colon and abnormal colon, malignant and premalignant, to predict the risk of developing colon cancer in high risk patients. Preliminary evidence suggests that cancer-associated alterations in colonic mucins may be due to incomplete glycosylation of the oligosaccharide chains. In studies proposed under grant, CA-30627, a factor which is released from specific tumor cells in vivo to the circulation and in vitro to culture medium is being identified and characterized and may form the basis for a general test for the presence of transformed and/or malignant cells.

Urinary nucleoside breakdown products of tRNA are being measured in cancer patients in grant CA-25210 and the molecular mechanisms responsible for the increased excretion in cancer patients are being explored. In grant CA-14185 modified purines, pyrimidines, imidazoles and their nucleosides derived from the turnover of human RNA and from the nucleic acid anabolic processes and present in urine of cancer patients will be evaluated as possible quantitative tumor markers. Studies under grant CA-33777, are designed to investigate the potential of using glycosaminoglycans (GAG) excreted in the urine as markers for bladder cancer and for identification of high risk groups, particularly those exposed to bladder carcinogens such as B-naphthylamine in the workplace.

Gas chromatography of the colonic microbial metabolites in breath and fecal specimens is being performed in grant CA-29056 to test the hypothesis that these metabolites may be useful markers for increased risk of developing colonic cancer. A new grant, CA-33739, will attempt to clarify understanding at the molecular level of the processes by which porphyrin complexes may be effective in location and regression of tumors.

An International Symposium on the Pathophysiology of Plasma Protein Metabolism held in Pisa, Italy on October 11-12, 1982 was partially supported by grant CA-34821.

2. IMMUNODIAGNOSIS

The portion of the Diagnosis Program classified as Immunodiagnosis can be subdivided into projects dealing with circulating tumor antigens or markers, such as oncofetal antigens, hormones, enzymes, and glycoproteins; projects dealing with tumor associated antigens, research in localization of tumors by radioimmunodetection, studies of lymphocytes in host-tumor relationships, and projects dealing with antibodies to tumors whether they be monoclonal, xenogenic, or response of the cancer-bearing host.

The use of monoclonal antibodies produced by hybridomas is an exciting new development in the area of immunodiagnosis. Much of the work that has been started with xenogenic antiserum produced in a variety of experimental animals is now being repeated with monoclonal antibody which has the distinct advantage of being specific for a single antigenic epitope. This has led to a new look

at previously known tumor markers of all kinds and has stimulated a renewed effort toward the identification of new tumor associated antigens. Monoclonal antibodies are also being probed for their potential in more accurate classification of tumors and are being radioactively labelled to exploit their value in tumor localization and therapy. Recently an announcement was issued by the program exploiting the use of monoclonal antibodies in the development of sensitive quantitative assays which could accurately identify and monitor levels of various isoenzymes that have been shown to be quantitatively increased in in certain cancers.

The recent identification of certain genetic sequences "oncogenes" which when rearranged by a virus or mutated by an environmental factor may activate production of specific gene products which can transform a cell to malignancy represents yet another exciting area with potential for diagnosis. An announcement to probe the potential of such research will be publicized in FY 1983.

The carcinoembryonic antigen is the most widely utilized circulating onco-fetal tumor marker. Several studies are concerned with elucidating its pathophysiology and metabolism. There is an ongoing study on the heterogeneity of CEA under grant CA-24376 which seeks to identify and isolate antigenic variants of CEA of the human digestive system. Comparison of new gastrointestinal cancer antigens with CEA and improvement of their clinical use is being undertaken in program project grant CA-04486. A multi-centre, randomized, controlled clinical trial involving 1500 patients is being conducted under grant CA-32302 to ascertain whether a policy of CEA prompted second-look surgery following "curative" resection of colo-rectal cancer will produce a decrease in morbidity and mortality due to tumor recurrence.

Several projects are investigating the relationship between hormone levels and cancer. A study of serum calcitonin as a screen for family members of patients with medullary thyroid cancer (MTC) is supported by grant CA-22595. Calcitonin studies have identified 28 patients with the sporadic type and 75 patients with dominantly inherited MTC. The role of serum thyroglobulin levels as predictors of tumor recurrence in thyroid cancer is being investigated under grant CA-25338. Preliminary data is indicating that serum thyroglobulin levels can reflect and predict total body iodine scan data. Tumor production of the neurohypophysial principles (vasopressin, oxytocin, vasotocin and their associated neurophysins) will be measured in plasma using specific radioimmunoassays, under grant CA-19613, to assess their value in the diagnosis and monitoring of therapy in patients with small cell carcinoma of the lung.

Two studies are evaluating the immunodiagnostic significance of enzymes as cancer discriminants. The objective of grant CA-34880 is to develop an immunohistochemical technique for the visualization of a monocyte esterase marker to be employed in the differential diagnosis of subtypes of leukemias. The goal of grant CA-25088 is to ascertain by immunochemical means if specific types of cancer can in part be detected by measurement of RNases in urine and sera which are presumably released by malignant tissues. Human pancreatic ribonuclease has been purified and characterized. Antibodies have been developed and an RIA developed. Immunological assay of normal and abnormal serum samples has been initiated.

Proteins or their degradation products have been detected in body fluids and have demonstrated correlation with the presence of cancer. The role of SAA, a serum alpha globulin and a major protein constituent of secondary amyloidosis is being investigated as a marker of tumor recurrence, response to therapy and immune function in cancers of the lung and gastrointestinal tract in grant CA-22141. Preliminary data suggests that SAA may cause immunosuppression by affecting T-cell macrophage interaction. Gp 48, a major group of glycoproteins synthesized and released into organ culture from breast adenocarcinoma specimens, are being characterized and assessed for their diagnostic significance in grant CA-24645. Studies are continuing under grant CA-31762 to biochemically characterize a glycoprotein surface antigen found on myeloblasts of leukemia patients, prepare antiserum to it and monitor its efficacy in predicting relapse of leukemia patients in remission. Monoclonal antibodies are being prepared and tested and surface antigen density studies of marrow cells are being performed.

Tumor associated antigen studies are under way for many organ sites: urogenital tract, CA-27213; melanoma, CA-30019 and CA-20364; mesothelioma, CA-27081; gastrointestinal tract, CA-30209; colon CA-26246; and leukemia CA-19304. The approach in grant CA-34187 is to determine whether indirect immunofluorescence and immunoperoxidase procedures with monoclonal antibodies developed against human melanoma antigens can localize tumor associated antigens in cryostat and paraffin sections of tumor specimens. The diagnostic and prognostic value of monoclonal antibodies that bind to human prostate adenocarcinoma membrane antigens are being studied under grant CA-27623. Studies of nuclear antigens associated with normal and leukemic human blood cells to determine their usefulness as markers in hematopoiesis are being supported by grant CA-26948. The overall objective of grant CA-32245 is to define and characterize human sarcoma-related mesenchymal antigens with monoclonal antibodies and to use such antigen markers for the differential diagnosis of human sarcomas. Identification of "pre-malignant" cell populations will be attempted in a new study grant, CA-34635, in which monoclonal antibodies will be produced to "pre-malignant cells" to determine the tissue localization at different stages of chemical hepatocarcinogenesis in rats. Immunolabeling will then be used to isolate the presumptive malignant cells and their malignant potential determined by transplantation to syngeneic rats. The aim of CA 33767 is to investigate the biological function of endogenous bombesin-like peptides in oat cell carcinoma. These have been found in the normal lung in low densities while in human small (oat) cell lung cancer (SCLC) biopsy tissue and cells in culture the density of immunoreactive bombesin is elevated up to three orders of magnitude. They were not detectable in other cancers or in the non-small cell cancer studied. Thus, they may serve as unique biochemical markers to monitor the progression of SCLC.

Some innovative approaches will be used in a new grant CA-35227. An attempt will be made to characterize human myeloid leukemia cells using murine and human hybridoma technology to a state of high reproducibility and may, with their new methodology, eliminate the need for somatic cell hybridization that is now a requirement for human monoclonal antibody production. The potential exists in another new grant, CA-34782, of developing some very useful antibody reagents. Antibodies specific for the three classes of pyrimidine dimers formed by UV-irradiation of DNA will be developed and incorporated into immunohistochemical monoclonal antibody techniques. These investigators have improved their human

procedures that will allow the rates of induction, distribution and fate of DNA damage to be measured in mouse epithelial cells exposed *in vivo* to UVR. This could later be applied to screen and identify DNA-repair deficiencies in high risk individuals of families with a high susceptibility to skin carcinogenesis.

Several studies are exploiting techniques of labeling antibodies with radio-nuclides for tumor detection and localization. Grant CA-30255 is directed towards immunolocalization of germ-cell tumors and hepatomas which produce alphafetoprotein by labeling of monoclonal antibodies with ¹³¹Iodine, ⁹⁹Tech-netium and ¹¹¹Indium. An approach is being tested under grant CA-28462 to develop an optimum technique for labeling antibodies to human serum albumin (HSA) with ¹¹¹In or ⁹⁹Tc or ¹²⁸I, and determine the relationship between accelerated blood clearance and retention of immunological activity. The objec-tive of grant CA-17742 is to study conditions favoring the localization of CEA-containing human tumors in animal systems by means of radiolabeled anti-CEA immunoglobulins and total-body photoscanning. The potential value of binary antibody combinations (AFP and CEA) in tumor localization are now being tested. Grant CA-25584 is a continuation of the program of CEA-tumor radioimmuno-detection and involves planning a clinical trial of patients with proven malignancy to further evaluate its use in initial tumor diagnosis and in the management and clinical staging of cancer patients. In a comparison made with other tumor detection methods by this investigator, radioimmuno-detection appeared to be superior to computed tomography, conventional liver scintigraphy and ultrasono-graphy, especially in the detection of confirmed liver metastasis. Pilot studies with rabbit antibody against prostatic acid phosphatase have also demonstrated that prostatic carcinoma, both primary and metastatic, can be disclosed by this approach. Grant CA-29639 concerns itself with the development of a method for melanoma localization using radiolabeled monoclonal antibody and Fab fragments against p97 antigen and then imaging by emission tomography. Studies conducted under grant CA-31236 are evaluating the role and accuracy of radiolabeled anti-AFP and anti-hCG in detecting testicular cancer using total-body scintigraphy. Preliminary results indicate the successful imaging of AFP-producing tumors with radiolabeled anti-AFP monoclonal antibody. The role and accuracy of radio-immuno-detection of colorectal cancer using colon specific antigen-p (CSAp) as the target are subjects for investigation under grant CA-31756. It appears that CSAp radioimmuno-detection has a high level of sensitivity in patients with colorectal, both primary and metastatic.

Lymphocytes and monocytes in host tumor responses are the subject of several projects. The development of clinically useful diagnostic tests based on the selective binding of bacteria and antibody-coated bacteria to lymphocyte sub-populations is being undertaken under grant CA-29552. Grant CA-21399 aims to elucidate the relationship between the natural binding of bacteria to lympho-and contribute greatly to an understanding of the immunobiology of the lymphoid malignancies are being pursued under grant CA-30020. The objective is to develop a comprehensive classification of human lymphomas based upon B and T cell lineage and subset specificity using monospecific hybridoma T cell reagents. Clinical course and response to treatment will be correlated with the membrane antigen phenotype of these cells and the histopathological examinations of the specimens. cytes and lymphocyte function. Studies which may be of prognostic value

and contribute greatly to an understanding of the immunobiology of the lymphoid malignancies are being pursued under grant CA-30020. The objective is to develop a comprehensive classification of human lymphomas based upon B and T cell lineage and subset specificity using monospecific hybridoma T cell reagents. Clinical course and response to treatment will be correlated with the membrane antigen phenotype of these cells and the histopathological examinations of the specimens.

Investigations of the expression of the major virion glycoprotein gp52 of MMTV on late-occurring mammary tumors in mice and its potential as a tumor marker are being pursued under grant CA-34711. Studies under grant CA-18404 seek to elucidate the evolution of cell populations with neuroendocrine differentiation in human lung cancers. Cell surface iodination techniques and 2-dimensional polyacrylamide gel electrophoresis are being used to search for distinguishing cell surface phenotypes of the different histologic types of lung cancers. Monoclonal antibodies developed to these individual antigens could serve as immunologic probes for improved detection and management of this disease.

The aim of studies under CA-34765 are to transfect mouse cells with human transforming genes from Hodgkins' disease, neuroblastoma and AML and prepare monoclonal antibodies to the transforming gene products or proteins induced by them. The hypothesis proposed is that the protein products of transforming genes of human tumors are essential elements of the malignant state and antibodies produced to them may be useful in the diagnosis and therapy of malignancies.

In addition to the research grants, there are contracts for the collection, storage and distribution of serum samples from patients with cancer and other acute and chronic diseases and during the course of therapy. These contracts, CB-74213, CB-74138, CB-84258 and CB-84296, have been invaluable for the rapid evaluation of a wide variety of serologic biochemical and immunodiagnostic tests for cancer that come to the attention of NCI. Two contracts, CB-14359 and CB-14339 support the statistical services which are required for the Serum Bank programs. A tissue culture bank for cell lines which can be utilized by investigators for research in cancer immunodiagnosis is maintained under contract CB-14351.

The availability of frozen sera, from patients with various malignancies, which are collected and maintained at the Mayo-NCI Serum Bank (CB-84258) has led to the initiation of a multi-institutional study on "Use of Multiple Markers in Lung Cancer Diagnosis" involving three contracts (CB-23915, CB-23929 and CB-23930). These laboratories are performing multiple assays on aliquots of sera from the same patients, correlating results with clinical data and then in collaboration with NCI analyzing the collective results. The objective is to determine by appropriate multi-variant statistical techniques if a combination of markers can be found that will increase both the sensitivity and specificity of the test to the point of clinical utility for diagnosis and/or prognosis of lung cancer.

3. CYTOLOGY

Diagnostic cytology research projects include the development of automated instrumentation and cell markers that can be used to differentiate normal and atypical cells. Instruments undergoing development and testing are those of high resolution slide based types and flow fluorometric types.

Under grant CA-27313, new automated morphometric image analysis techniques are being developed to establish criteria for the identification and classification of cells in sputum; and under grant CA-32345, image processing techniques are being developed and applied to rapidly screen cells from voided human urine.

Classification of gynecologic cells based on computer analysis of their digitized images is continued under grant CA-13271; while a clinical trial using a high resolution image analysis system to analyze monolayers of Papanicolaou stained cells for detection of cervical cancer is supported under grant CA-31049. Single cell classification algorithms employing the current state of the art in digital image processing, scene segmentation and image acquisition hardware were originally developed and tested under a contract. This research has now been continued under grant CA-31718. An automated screening system has been designed and is under fabrication as a result of the cost/utility analysis which indicated that the chosen algorithms can operate with the performance sufficient to support cost-effective automated screening for cervical cancer. This system utilizes digital image analysis approach to analyze exfoliated epithelial cells. detection of cervical cancer is supported under grant CA-31049. Development, construction and testing of an ultrafast optical scanner for microscopic specimens, grant CA-24466, will significantly increase the speed for the automated search for abnormal or cytochemically marked cells in microscopic preparations. A prototype scanner is under fabrication and testing and should revolutionize the rate of data acquisition for image analysis technology.

The testing of a multidimensional slit-scan instrument which uses a combined static and flow system is continued under grant CA 30582. A spectrum of normal and abnormal gynecologic specimens are used. The study will determine the system characteristics including rate and causes of false alarms. The instrument is sensitive to the entire spectrum of abnormality of the cells tested. A new system of less complexity is also being developed. This system will provide the same multidimensional slit-scan information as the first instrument but substantially more rapidly and more accurately. The multidimensional slit-scan technology is also being applied to analyze exfoliated cells from the bladder epithelium to detect cancer of the urinary bladder, grant CA-33148. Currently the data base is being generated and expanded with the static instrument.

A system is under development to place individual sorted cells on slides for subsequent retrieval and analysis, grant CA-28706. This prototype, Cell Deposition System, will make possible the correlation of any cell sorted and its flow microfluorometric data; in addition, a fluid cell sorter is being designed under grant CA-32314. This cell sorter will be used in conjunction with the multidimensional slit-scan flow system mentioned above.

Chemical synthesis of cytochemical probes, grants CA-28770 and CA-30148, with sharp fluorescence emission spectra will enhance multiple staining of cells for flow systems and for cells on slides in static systems. Cell surface antigens may also be used as markers for abnormal cells. With appropriate fluorescent tagging of these antigens, normal and abnormal cells may be differentiated by automated instruments. Potentially useful markers being studied are Herpes simplex virus related antigens, grant CA-28724. These marker proteins are detected by fluorescently labeled secondary antibodies, flow microfluorometry, and light scattering cytometry. One HSV marker protein has been shown to be HSV-2 specific and is being investigated for its use in uterine cervical cell labeling. Also analysis of DNA, RNA, protein, nucleolar antigen and cell volume are explored under grant CA-28771 to identify atypical cells in clinical material.

In addition, cytochemical and biophysical probes applicable to flow cytometry and cell sorting of nuclear and cytoplasmic structure are being used to distinguish normal and malignant cells and to discriminate between cycling and noncycling cells, and between proliferating and quiescent tumor cells, grant CA-28704.

Flow cytometry is used in grant CA-27283 to develop an assay for early detection of transformed cells (by chemical carcinogens) differentially labeled with fluorescamine. Hyaluronic acid (HA) synthetase activity is found to be stimulated significantly during the early stages of transformation. The synthesis, organization and functional significance of surface-associated HA by transformed cells is also being investigated.

To better understand and treat lymphoproliferative disease, flow microfluorometric analysis of human lymphoid malignancies is under investigation, grant CA-23393. Malignant cell subpopulations are identified using correlated analysis of membrane antigens, DNA and light scatter signals. In addition, it is hoped that the ploidy and cell cycle kinetic parameter of these cells will aid in the diagnosis, classification, scheduling and monitoring of treatment and that the procedures used will allow detection of low levels of circulating neoplastic lymphoid cells. A combined flow cytometric cell-sorting autoradiographic technique is continued in grant CA-25348 to monitor acute leukemias of adults and children and to predict remission and evaluate treatment protocol. Flow cytometry is also used to classify acute and chronic leukemia and non-Hodgkin lymphomas based on quantitative measurement of nucleic acid content, chromatin structure, and immunologic parameters. Using fluorescence microscopy and flow microfluorometry in grant CA-27123, merocyanine 540 is employed to study leukemia to characterize the dynamic changes in the staining pattern during the clinical course and to isolate and characterize hematopoietic progenitor cells. The selective staining of leukemic cells and flow microfluorometry can be a useful adjunct to existing methods of monitoring the course of leukemia and for detection of relapse or remission. The procedure may also provide information concerning residual leukemic hemopoiesis during remission. Merocyanine 540 is also utilized to elucidate the relationship between dye binding and the transformed state of cells in grant CA-28921. Study of human leukemic and preleukemic blood and bone marrow using the soft agar culture techniques has continued, grant CA-17353, to characterize the status and prognosis of hematoproliferative disorders. Measurements of the quality and quantity of colony formation appear to provide useful indicators of disease status and progression as well as diagnosis and predictions concerning response to therapy of acute nonlymphocytic leukemias and preleukemic states.

In an effort to better understand gynecologic neoplastic lesions, a quantitative analysis of nuclear DNA content using Feulgen microspectrophotometry is continued under grant CA-34870. Determination of the nuclear DNA changes may reveal the correlation of the changes with regression, persistence and progression of squamous cancer of the uterine cervix. By determining the ploidy patterns, it is possible to differentiate neoplastic from non-neoplastic changes. Earlier findings of carcinoma-in-situ of lung, and bladder might be possible by using an immunocytologic technique being evaluated in grant CA-26863, to detect carcinoembryonic antigen on exfoliated cells. The data thus far indicate that cytologic examination with anti-CEA staining procedure may also increase the accuracy of screening body fluids for malignant cells, and that examination of

cytologic preparations for CEA using immunoperoxidase technique is a useful adjunct in the diagnosis of malignancy of certain sites:

The Ninth Conference on Analytical Cytology was partially supported by grant CA-32959.

4. PATHOLOGY

A new international classification of human pituitary adenomas based on electron microscopy and immunocytochemistry has been developed under grant CA-21905. Seven distinct entities of pituitary adenomas are recognized. To expand understanding of tumor behavior of head and neck cancer, especially pre-malignant changes distant from the primary growth, in the pyriform sinus and the oral cavity, whole organ sections of patients who undergo surgical excision have been studied, grant CA-22101, using microscopic appearance to determine size and extent of tumor, relation of tumor spread to the laryngeal framework and specific routes of tumor spread. Malignant lymphomas and leukemias are being studied on grant CA-26422 by a combination of methodologies including immunologic surface markers, monoclonal antibodies, cytogenetics, electron microscopy and flow microfluorometry to determine the most valuable tests to provide earlier detection and more precise classification. The study of abnormal differentiation of leukocytes to establish better methods for the diagnosis and classification of leukemias and lymphomas is continued under grant CA-14264. This study involves light and electron microscopy, immunohistochemistry and tissue culture. Using pathological specimens, various tumor markers including estrogen and progesterone receptors, CEA, HCG, AFP, are being evaluated in grant CA-29211 to study endometrial and cervical carcinoma. Better diagnostic methods for subclassification of bronchioalveolar carcinomas are being studied under grant CA-33717. This project will provide a more accurate prognosis, and better selection of treatment modality.

5. MULTIPLE DISCIPLINES

Five contracts and five grants involving several disciplines are presented in this last category. Grant CA 25582 is developing instrumentation and procedures for fluorescence bronchoscopy to localize very small areas of mucosal carcinoma and evaluating photoradiation therapy with porphyrin derivatives. Genetic markers for multiple endocrine neoplasia, Type II (MEN), are studied under grants CA 32066 and CA 35040. These studies aim at establishing genetic linkage between a polymorphic marker and the presumed locus for MEN, and screening to detect preclinical onset of disease. A long term following of the patients, clinically and biochemically, may establish the natural history of the disease. Grant CA-35040 is also evaluating chemotherapy for familial medullary carcinoma of thyroid and pheochromocytoma. Grant CA-35966 attempts to identify and map cancer susceptibility genes in man. Large cancer families are studied with respect to a wide variety of biochemical and DNA markers.

To improve the quality of endoscopic examinations for early detection and diagnosis of cancer, videotape programs are being further developed under grant CA-33618. The programs should enhance visual discrimination skills, and at present include upper airway, lungs, esophagus, stomach, duodenum and colon.

A collaborative study is continued under contracts CN-45007, CN-45037 and CB-53886 to determine the effect on lung cancer mortality resulting from the addition of sputum cytology screening to radiographic screening compared to screening by radiography alone. A fourth related contract, CB-43868, is concerned with the data management and combined data analysis of the collaborative early lung cancer study. The study, which was begun in 1974, involves 30,000 men. The screening phase has been concluded and the study is currently in the follow-up phase.

A large-scale longitudinal colon cancer screening study using the Hemocult test for human blood in the feces is the task of contract CB-53862. Several more years of follow-up on the 45,000 subjects will be required to define the usefulness of the screening procedure in detecting early colorectal cancer and whether this will result in a reduction in mortality from that disease.

Publications

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1. BIOCHEMISTRY

- R01-CA-14185 Modified Nucleosides in Cancer and Normal Urines
Girish Chheda Roswell Park Memorial Institute
- R01-CA-14380 Pancreatic Ductal Versus Duodenal Secretions
Thomas T. White University of Washington
- R01-CA-22599 Programs of Normal and Malignant Lymphocytes
Allen E. Silverstone Sloan-Kettering Institute for Cancer Research
- R01-CA-23945 Assessment of Malignancy in Human Chondrosarcomas
Lawrence C. Rosenberg Montefiore Hospital and Medical Center
- R01-CA-25210 Origins of Urinary Nucleosides in Tumor Tissue
Ernest Borek AMC Cancer Research Center
- R01-CA-25376 Development of Serum Nuclease Isozyme Test for Cancer
Kwan C. Tsou University of Pennsylvania
- R01-CA-29056 Large Bowel Cancer & Colonic Microbial Metabolism
David A. Mastromarino University of Texas
- R01-CA-29062 Vasoactive Intestinal Peptide in Diagnosis of Leukemia
Mary S. O'Dorisio Ohio State University
- R01-CA-30627 In Vivo Release of Transformed Cell-Specific Proteins
Thomas E. Webb Ohio State University
- R01-CA-30667 A Study of Cancer Associated Colonic Mucin
Clement R. Boland University of California, San Francisco
- R01-CA-30687 Progesterone-Specific Protein in Endometrial Secretions
George S. Richardson Vincent Memorial Hospital
- R01-CA-31218 Thyrotropins from Tumors of Trophoblastic Origin
Syed M. Amir Beth Israel Hospital
- R01-CA-32585 Creatine Kinase BB as a Tumor Marker
Gerald B. Dermer University of North Carolina
- R01-CA-33207 Calcitonin in Thyroid Carcinoma
George D. Sorenson Dartmouth Medical
- R01-CA-33615 Multiple Forms of HGH: Measurements and Actions
Willard Vander Laan Whittier Institute for Diabetes & Endocrinology
- R01-CA-33739 Porphyrins in Cancer Treatment: Molecular-Level Studies
Rimona Margalit Tel-Aviv University
- R01-CA-33777 GAG as Bladder Cancer Markers in High-Risk Population
Robert E. Hurst University of Alabama in Birmingham

R13-CA-34821 Symposium on Plasma Protein Metabolism
Joseph J. Di Stefano University of California

R01-CA-34881 Biochemical and Clinical Application of Acid Phosphatase 5
Kwok-Wai Lam University of Texas Health Sciences Center

2. IMMUNODIAGNOSIS

P01-CA-04486 Pathology of the Digestive Tract Mucous Membrane
Norman Zamcheck Boston City Hospital

R01-CA-17742 Radiological Localization of Human Tumors
David M. Goldenberg University of Kentucky Medical School

R01-CA-18404 Neuroendocrine Differentiation in Human Tumors
Stephen Baylin Johns Hopkins Medical Institution

R01-CA-19304 Human Leukemia & Lymphoma Associated Antigens
Ben Seon Roswell Park Memorial Institute

R01-CA-19613 Ectopic Hormones in Small Cell Carcinoma of the Lung
William G. North Dartmouth College

R01-CA-20364 Immunodiagnosis of Mesothelioma
Hilliard F. Seigler Duke University

R01-CA-21399 Binding of Bacteria to Normal & Leukemic Lymphocytes
Marius Teodorescu University of Illinois Medical Center

R01-CA-22141 Protein SAA in Neoplastic Disease
Merrill D. Benson Indiana University School of Medicine

R01-CA-22595 Detection of Medullary Thyroid Cancer in Families
Charles E. Jackson Henry Ford Hospital

R01-CA-24376 Immunological Heterogeneity of CEA
James F. Primus University of Kentucky

R01-CA-24645 Significance of GP48 in Diagnosis of Breast Cancer
Zoltan A. Tokes University of Southern California

R01-CA-25088 Human Ribonucleases and Cancer
Dohn G. Glitz University of California, Los Angeles

R01-CA-25338 Thyroglobulin Radioimmunoassay in Patients with Thyroid Cancer
Merl A. Charles University of California, Irvine

R01-CA-25584 Clinical CEA-Tumor Radioimmunoassay
David M. Goldenberg University of Kentucky

R01-CA-26246 Assay of Human Tumor or Organ-Associated Antigens
Calvin A. Saravis Boston City Hospital

R01-CA-26948 Nuclear Antigens as Markers in Hematopoiesis
Robert C. Briggs Vanderbilt University

R01-CA-27081 Immunodiagnosis of Mesothelioma
Gurmukh Singh University of Pittsburgh

R01-CA-27213 Detection of Urogenital Normal and Neoplastic Antigens
Robert W. Green Duke University Medical Center

R23-CA-27623 Characterization of Prostate Cell Plasma Membranes
James J. Starling Eastern Virginia Medical Authority

R01-CA-28462 Radiolabeling of Tumor Antibodies
William C. Eckelman George Washington University

R01-CA-29552 Differential Counting of Lymphocyte Subpopulations
Marius Teodorescu University of Illinois Medical Center

R01-CA-29639 Tumor Imaging with Radiolabeled Monoclonal Antibody
Steven M. Larson VA Medical Center

R01-CA-30019 Purification of Tumor Antigens of Defined Specificities
Rishab K. Gupta UCLA Center for Health Sciences

R01-CA-30020 The Cell Surface Phenotype of Malignant Lymphoma
Alan C Ainsenberg Massachusetts General Hospital

R01-CA-30209 Immunochemical Studies of Gastrointestinal Cancer
Elliott Alpert Baylor College of Medicine

R01-CA-30255 Immunolocalization of Human Malignant Tumors
Elliott Alpert Baylor College of Medicine

R01-CA-31236 AFP/HCG Radioimmuno-detection in Testicular Cancer
David M. Goldenberg University of Kentucky

R01-CA-31756 CSAP Radioimmuno-detection of Colorectal Cancer
David M. Goldenberg University of Kentucky

R01-CA-31762 Immunologic Diagnosis of Myeloblastic Leukemia
Robert N. Taub Columbia University School of Medicine

R01 CA-32245 Detection & Characterization of Mesenchymal Antigens
Yashar Hirshaut Sloan-Kettering Institute for Cancer Research

R01-CA-32302 Controlled Trial: CEA Prompted 2nd Look in Bowel Cancer
William R. Slack University of London

R01-CA-33767 Bombesin-Like Peptides in Oat Cell Carcinoma
William Terry Moody George Washington University

- R01-CA-34039 Carbohydrate Determinants as Human Tumor Markers
Kenneth O. Lloyd Sloan-Kettering Institute Cancer Research
- R01-CA-34187 Monoclonal Antibodies in Diagnosis & Prognosis of Cancer
Darwin O. Chee Scott Laboratories, Inc.
- R01-CA-34635 Preneoplastic Markers Detected by Monoclonal Antibodies
Stewart Sell University of Texas Science Center at Houston
- R01-CA-34711 Viral Proteins: Possible Systemic Signals for Tumors
Earl M. Ritzi Oklahoma College of Osteopathic Medicine
- R01-CA-34765 Specificity of Antitransforming Gene Product Antibody
Marshal Dore Sklar St. Jude Children's Research Hospital
- R01-CA-34782 Immunological Detection of Pyrimidine Dimers in Situ
Ronald D. Ley Lovelace Medical Center
- R01-CA-34880 Clinical Application of Esterase, a Monocyte Marker
Kwok-Wai Lam University of Texas Health Sciences Center
- R01-CA-35227 Human and Murine Hybridoma Antibodies in Acute Leukemias
Lennart Olsson State University Hospital, Copenhagen, Denmark

3. CYTOLOGY

- R01-CA-13271 Automated Cancer Cell Diagnosis by the TICAS Method
George Wied University of Chicago
- R01-CA-17353 Marrow Culture Studies in Human Myeloid Leukemias
Malcolm A. Moore Sloan-Kettering Institute for Cancer Research
- R01-CA-23393 Flow Analysis of Human Malignant Lymphoid Cells
Raul C. Braylan University of Florida
- R01-CA-24466 Ultrafast Scanner Microscope in Laboratory Automation
Roland V. Shack University of Arizona
- R01-CA-25348 Flow Cytometry/Autoradiography Monitoring of Leukemia
Michael Andreeff Sloan-Kettering Institute for Cancer Research
- R01-CA-26863 Identification of CEA in Cytology Specimens
Robert R. Pascal St. Luke's-Roosevelt Institute for Health Sciences
- R01-CA-27123 Application of Fluorescent Probes to Clinical Cancer
Jay E. Valinsky Rockefeller University
- R01-CA-27283 Early Detection of Transformed Cells
Susan P. Hawkes Michigan Molecular Institute

R01-CA-27313 A Search for Pre-neoplastic Cell Markers in Sputum
Stanley Greenberg Baylor College of Medicine

R01-CA-28704 Chromatin Probes for Distinguishing Malignant Cells
Zbigniew Darzynkiewicz Sloan-Kettering Institute for Cancer Research

R01-CA-28706 Cell Positioning System: Development and Use in Cancer
Harry W. Tyrer Cancer Research Center

R01-CA-28724 Biophysical Probes for Malignant Cells
Paul Todd Pennsylvania State University

R01-CA-28770 Biophysical Probes for Automated Cytology
Kwan C. Tsou University of Pennsylvania

R01-CA-28771 Cytology Automation
Barthel Barlogie M. D. Anderson Hospital and Tumor Institute

R01-CA-28921 Merocyanine Dyes as Leukemia-Specific Probes
Robert A. Schlegel Pennsylvania State University

R01-CA-30148 Development of Lanthanide Fluorescent Stains
Lidia M. Vallarino Virginia Commonwealth University

R01-CA-30582 Multistage Slit-Scan Prescreening System
Leon L. Wheelless University of Rochester Medical Center

R01-CA-31049 Clinical Test for Automated Prescreening Device
George L. Wied University of Chicago

R01-CA-31718 Automated Cytology Prototype Development
Kenneth R. Castleman California Institute of Technology

R01-CA-32314 Fluid Cell Sorter
Leon L. Wheelless University of Rochester

R01-CA-32345 Computer Image Analysis of Cells in Urothelial Cancer
Leopold G. Koss Montefiore Hospital and Medical Center

R13-CA-32959 Ninth Conference on Analytical Cytology
L. S. Cram Los Alamos National Laboratory

R01-CA-33148 Multidimensional Slit-Scan Detection of Bladder Cancer
Leon L. Wheelless University of Rochester

R01-CA-34870 Nuclear DNA Study of Gynecologic Cancers
Yao S. Fu University of California, Los Angeles

4. PATHOLOGY

- R01-CA-14264 Pathology of Cell Differentiation in Leukemia
Dorothy F. Bainton University of California, San Francisco
- R01-CA-21905 Pituitary Adenomas: Structure-Function Relations
Calvin Ezrin Cedars-Sinai Medical Center
- R01-CA-22101 Study of Head and Neck Cancer by Serial Section
John A. Kirchner Yale University
- R01-CA-26422 Clinico-Biologic Correlation in Lymphoma and Leukemia
Henry Rappaport City of Hope National Medical Center
- R01-CA-29211 Immunohistologic Study of Uterine Cancer
Clive R. Taylor University of Southern California
- R01-CA-33717 Bronchioloalveolar Carcinoma: Diagnosis and Pathobiology
Gurmukh Singh University of Pittsburgh

5. MULTIPLE DISCIPLINES

- R01-CA-25582 Fluorescence Endoscopy and Photoradiation Therapy
Oscar J. Balchum University of Southern California
- R01-CA-32066 Genetic Linkage in Multiple Endocrine Neoplasia, Type II
Joseph M. Gertner Yale University
- R01-CA-33618 Preclinical Training in Endoscopic Programs
John E. Rayl VA Medical Center Lake City, Florida
- R01-CA-35040 Early Detection of Medullary Thyroid Carcinoma
Naquib A. Samaan University of Texas System Cancer Center
- R01-CA-35966 MHC and Cancer Susceptibility Genes in Man
Richard A. Gatti University of California, Los Angeles

CONTRACT RESEARCH SUMMARY

Title: Human Tumor Cell Line Bank for Diagnostic Studies

Principal Investigator: Dr. Robert J. Hay
Performing Organization: American Type Culture Collection
City and State: Rockville, MD

Contract Number: N01-CB-14351
Starting Date: 9/29/81

Expiration Date: 9/28/86

Goal: The objectives of the program are to acquire, characterize, catalog, store and distribute a variety of cell lines having special utility for research in tumor diagnosis. Well characterized lines from solid tumors as well as from normal tissues will be included. Information concerning properties and utility of these lines will be provided to all interested investigators.

Approach: Cell lines selected in consultation with the Government Project Officer (GPO) and advisors will be expanded from token holdings or new submissions to produce seed and distribution stocks. These will be characterized using published ATCC procedures. Initially, standard tests for absence of microbial contamination will be applied and species verification will be accomplished by assay for the isoenzymes of glucose-6-phosphate dehydrogenase, lactic dehydrogenase and nucleoside phosphorylase. Distribution will begin upon satisfactory completion of these tests. Lines in the existing bank will be characterized further with regard to isoenzyme profiles, karyology, surface antigens, etc. as time and funds permit.

Progress: Of the lines selected for transfer by the advisory committee, 100 were suitable for cataloguing, banking and distribution. Accordingly, characterized stocks of these have been included in the 1983 edition of the ATCC Catalogue II and all are currently being distributed. Lines of highest distribution are being characterized further. Token stocks on some 965 human cell lines have been received from The Naval Biosciences Laboratory in Oakland, California. Their credentials have been reviewed in part, and pertinent details were tabulated to provide an initial basis for decisions on which should be included in this bank. Selections will be made upon joint consultations between the GPO, advisors and ATCC scientists. Fifteen breast cancer cell lines were also shipped to ATCC from the EG&G Mason Research Institute for inclusion into the Human Tumor Cell Line Bank. Lines are shipped for a fee upon request. Cell line shipments are averaging approximately 30 per month for first three months of 1983.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 83 Funds: \$140,640

A

CONTRACT RESEARCH SUMMARY

Title: Biological Markers in Breast Cancer: Patient Resource

Principal Investigator: Dr. Theodore Maycroft
Performing Organization: Butterworth Hospital
City and State: Grand Rapids, MI

Contract Number: N01-CB-23927

Starting Date: 9/15/77

Expiration Date: 1/31/84

Goal: To develop a specimen resource for blood from breast cancer patients, benign disease patients and controls to be used in a search for and verification of new breast cancer markers.

Approach: Thirty milliliters of blood are collected prior to surgery from patients who are scheduled to undergo biopsy and/or primary surgery for breast lesions and processed into 10-15 ml aliquots of serum. Specimens are collected also in the early post-mastectomy period. Annual drawings are made on patients with malignant diagnosis. Patients with benign tumors are requested to complete annual questionnaires for a period of two years after biopsy. Serum specimens are stored at -70°C , then shipped to an NCI designated blood bank facility. Appropriate clinical data is sent to central data center.

Progress: Since the inception of the program, more than 3,000 patients have been entered into the study. Approximately 52,000 vials containing serum specimens have been shipped to the central storage facilities at Mayo Clinic. Collections have been made on the annual anniversary of malignant patients and follow-up questionnaires have been completed on patients with benign lesions. This information has been forwarded to the Data Center. The participating surgeons and personnel from the collaborating hospitals have continued to give excellent cooperation with the biomarkers project staff.

Project Officer: Ihor J. Masnyk, Ph.D.
Program: Diagnosis
FY 83 Funds: \$49,318

A

CONTRACT RESEARCH SUMMARY

Title: Biologic Markers in Breast Cancer: Patient Resource

Principal Investigator: Dr. Ned D. Rodes
Performing Organization: Cancer Research Center
City and State: Columbia, MO

Contract Number: N01-CB-23925
Starting Date: 9/01/77
Expiration Date: 5/31/83

Goal: To serve as a specimen resource for blood from breast cancer patients and controls to be used in search for and verification of new breast cancer markers.

Approach: 30 ml of blood are collected from volunteer Breast Cancer Detection Project and Women's Cancer Control Program patients after they have signed appropriate consent forms and processed into 10-15 1 ml aliquots of serum. In the event of subsequent malignant breast biopsy, a 30 ml specimen is also collected post-mastectomy within three months. In addition, pre-biopsy and post-mastectomy blood samples will be obtained from hospitalized women in the Columbia area who agree to participate in the program. Emphasis is now placed upon the collection of samples from symptomatic patients rather than specimen collection from normal volunteer screenees. Anniversary serum from malignant patients will be obtained for three, possibly five years, and annual clinical history from patients with benign biopsies. All blood will be stored at -70° centigrade, and then shipped to NCI-designated serum storage facility. Appropriate clinical data will be sent to central data center.

Progress: The primary emphasis for the Cancer Research Center Serum Collection Unit is to obtain serum samples pre-operatively from patients with benign breast disease, and pre- and post-operative malignant breast disease samples. Along with this, samples from normal participants and annual follow-ups were continued to be collected. The Cancer Research Center Serum Collection Unit collected 136,825 vials of serum from 7,276 participants who donated 12,610 individual samples (many patients were repeat donors in accordance with the protocol). Careful follow-up was maintained on the apparently normal volunteers, which makes this bank unique world-wide.

Project Officer: Ihor J. Masnyk, Ph.D.
Program: Diagnosis
FY 83 Funds: \$23,420

A

CONTRACT RESEARCH SUMMARY

Title: Data Management System for NCI Serum Panels

Principal Investigators: Dr. Lee A Richman and
Dr. C.M. Dayton
Performing Organization: Ebon Research Systems
City and State: Washington, DC

Contract Number: N01-CB-14359

Starting Date: 8/08/77

Expiration Date: 2/07/84

Goal: To provide data management and statistical programming support for re-search projects being conducted by the Diagnosis Program through the NCI Serum Bank in order to determine which serum assays are best for early detection, diagnosis, and prognosis.

Approach: To perform statistical analyses of laboratory and clinical data from NCI serum panels, and to prepare summary reports of the results.

Progress: During the past year further improvements were made in the analytic approach for evaluating cancer panels, particularly since precoded clinical data now are being supplied by the Mayo Clinic. Analyses now can include age, sex, primary diagnosis, stage, cell type, grade, date of surgery, smoking category, amount smoked per day, years smoked, tumor status, and, in some cases, secondary and tertiary diagnosis.

Since March 5, 1982, Ebon has completed two serum panel analyses, including one multiple assay. Analyses of Monoclonal Antibody (CA 19-9) plus Carcino-embryonic Antigen (CEA), also Fast Homoarginine Sensitive Alkaline Phosphatase assays were conducted, and an additional analysis is in progress for a panel analyzing levels of secretory IgA by the enzyme-linked immunosorbent assay.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 83 Funds: 0

A

CONTRACT RESEARCH SUMMARY

Title: Biomedical Computing Software Support to Breast Cancer Markers Program

Principal Investigator: Ms. Marlene Dunsmore
Performing Organization: Information Management Services, Inc.
City and State: Bethesda, MD

Contract Number: N01-CB-14339

Starting Date: 3/31/81

Expiration Date: 3/30/84

Goal: To increase the usefulness of the data generated in projects related to the diagnosis of human breast cancer.

Approach: A central file was developed by the contractor for breast tumor biomarkers program. The file allows preparation of various serum panels for testing new biological markers for breast cancer, setting up studies on multiple markers involving multiple institutions, and comparisons of the results from various studies and provides a data base from which material can be quickly and conveniently retrieved. This data file is also intended for testing new ideas, identifying groups of subjects suitable for more detailed study and for preparing reports to the medical community and the general public.

Progress: Communication with the collaborating institutions has been maintained. The main file update system modifies clinical history files with new information and continues to edit for data consistency. In support of the Biological Markers Project, background and clinical data have been gathered for 175,500 blood collections from three institutions. Benign tumor and metastatic cancer follow-up information continues to be submitted. Although the availability of the sera has not yet been officially announced, several requests have been received and approved. The Data Center has prepared the lists of coded samples and evaluated the laboratory results submitted by the investigators.

Project Officer: Ihor J. Masnyk, Ph.D.
Program: Diagnosis
FY 83 Funds: \$164,598

A

CONTRACT RESEARCH SUMMARY

Title: Lung Cancer Control: Detection and Treatment

Principal Investigator: Dr. John K. Frost
Performing Organization: Johns Hopkins University
City and State: Baltimore, MD

Contract Number: N01-CN-45037
Starting Date: 1/01/73
Expiration Date: 7/15/84

Goal: To determine the effect on lung cancer mortality due to early detection by sputum cytology followed by surgical removal of the tumor.

Approach: 10,387 males who were 45 years or older and had smoked a pack or more of cigarettes a day were randomly assigned to one of two groups: the "X" group receives an annual chest x-ray only; the "CX" group receives an annual chest x-ray, an annual sputum induction plus a sputum cytologic examination every four months. All subjects are followed after final screening to determine actuarial survival.

Progress: 5161 men were randomized into the "X" group and 5226 into the "CX" group. To date, 1345 have died, while 2557 have withdrawn from the study or moved from the area. Currently 6400 remain as active participants, 3278 in the "X" group and 3122 in the "CX" group. At the initial screening, 79 cancers were detected (40 in the X group and 39 in the CX group) for a "detected prevalence" of 7.6 per 1000. Following an initial screening, a total of 337 cancers appeared (175 in the X group and 162 in the CX group) for an "annual incidence" of 5.4 per 1000 person years. In the CX group, 57 (63%) incidence cases were detected at AJC Stage I, 10 (11%) of these were in situ and 3 (3%) were microinvasive, and 44 (49%) invasive; 72 additional cases occurred between screenings, 11% at Stage I. In the X group, 49 (53%) incidence cases were detected at AJC Stage I, all invasive; 82 additional cases occurred between screenings, 19% at Stage I. Among the 162 cases occurring in the CX group after initial screening, 68 (42%) were resected; 69 (39%) of the 175 incidence cases occurring in the X group were resected. In the screened population, 416 total lung cancers have appeared: 215 in the X group and 201 in the CX group. Among the 215 cases of lung cancer found in the X group, 156 (72%) have died; of the 201 lung cancer cases in the CX group, 132 (66%) have died. Although the mortality rates of cancers detected at first screening and the mortality rates of cancers detected at subsequent screening show reduced mortality for the CX group, separately these comparisons fail to reach statistical significance. However, when the total number of lung cancer deaths which have occurred are combined over all age groups and appropriately weighted the overall mortality due to lung cancer among the CX group is significantly lower than that of the X group. The observation of a reduced lung cancer mortality in the CX group seems likely to be due to a slight excess of new cases in the X group and an unusual XC/X cell type distribution rather than to the effect of cytologic screening, early detection and therapy. The entire benefit of cytologic screening seems to be confined to only one cell type (squamous).

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 83 Funds: \$642,381

A

CONTRACT RESEARCH SUMMARY

Title: NCI Sera Bank Facility: Biological Markers in Breast Cancer

Principal Investigator: Dr. Vay Liang Go
Performing Organization: Mayo Clinic Foundation
City and State: Rochester, MN

Contract Number: N01-CB-33931
Starting Date: 2/01/83 Expiration Date: 1/31/84

Goal: To establish and maintain a storage facility for serum specimens to be used in a program designed to search for biological markers in breast cancer.

Approach: Serum specimens are secured from breast cancer patients, benign disease patients, apparently normal controls, and a screening population under separate contracts. The material is processed, recorded and stored in -70°C deep freezers under easily retrievable conditions. The sera will be used in the search for and verification of new breast cancer markers.

Progress: The bank consists of about 200,000 serum vials representing 18,350 donations from thousands of volunteers. Thirty seven freezers are continuously in operation, direct wired for alarm in case of a potential power failure. The logistics of specimen received, inventory and preparation of test panels have been fine-tuned to perfection. Several serum shipments were mailed out to field-test the procedures. The bank is ready.

Project Officer: Ihor J. Masnyk, Ph.D.
Program: Diagnosis
FY 83 Funds: \$122,000

A

CONTRACT RESEARCH SUMMARY

Title: Detection and Localization of Early Lung Cancer

Principal Investigator: Dr. Robert S. Fontana
Performing Organization: Mayo Foundation
City and State: Rochester, MN

Contract Number: N01-CB-53886
Starting Date: 9/27/74

Expiration Date: 9/26/84

Goal: To test new methods of diagnosis of early lung cancer and to assess survival of patients with lung cancer detected by these methods.

Approach: A study population of 9,211 subjects was obtained following initial screening of 10,935 non-volunteers. Candidates were Mayo Clinic outpatients who were men, 45 years old or more, smoking one pack of cigarettes or more daily. None of those accepted into the study had a history or suspicion of respiratory cancer on entry into the Clinic. Initial screening consisted of chest radiographs, 3-day sputum cytology tests and lung health questionnaires. This screening yielded 91 unsuspected ("prevalence") lung cancers, 17 detected by cytology alone, 59 by radiography alone, and 15 by both tests. Radiographically "occult" cancers were localized bronchoscopically. The 9,211 study subjects who had "negative" initial screens were randomized into a close-surveillance group of 4,618, for whom rescreening every 4 months was urged, and a standard surveillance ("control") group of 4,593 advised, but not reminded, to undergo rescreening once a year.

Progress: As of January 1, 1983 (backdated to January 1, 1982, to make the two study groups more comparable), the 4-monthly surveillance group and the control group had each been observed 32,000 man-years. A total of 368 new ("incidence") cases of respiratory cancer had been detected. Of these, 70 involved the upper airway and 298 the lungs. In the 4-monthly surveillance group there were more cancers, more early-stage cancers, more resectable cancers and better survivorship than in the control group. However the number of advanced cancers, unresectable cancers, and lung cancer deaths was approximately equal in the two groups. As incidence cases continue to accrue, more detailed analyses of data are feasible. Attention is currently being directed toward evaluation of the persistent disparity in the number of incidence cancers in the two study groups. Results of screening are being studied according to age groupings, tumor cell types, and methods of detection. Degree of "contamination" of the control group by radiologic "screening" for clinical reasons is also being investigated.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 83 Funds: 323,640

A

CONTRACT RESEARCH SUMMARY

Title: Maintenance of the NCI Serum Diagnostic Bank

Principal Investigator: Dr. Vay Liang W. Go
Performing Organization: Mayo Foundation
City and State: Rochester, MN

Contract Number: N01-CB-84258

Starting Date: 9/30/78

Expiration Date: 11/30/83

Goal: To establish and maintain a bank of frozen sera from patients with cancer, with benign diseases and from normal individuals, for evaluating immunodiagnostic and biochemical tests of potential clinical usefulness in the diagnosis of cancer.

Approach: Collect and make necessary serum samples available for evaluation of biochemical and immunodiagnostic tests for cancer. Serve as a central facility for storage of serum and plasma specimens collected by other contractors in the Diagnosis Program.

Progress: A bank of sera are established and maintained from patients with histologically diagnosed malignancies, benign diseases and healthy individuals, together with a computerized clinical data and inventory system. Sera are stored at -75°C for long-term storage with adequate continuous temperature monitoring and quality control. The sera are made available by the Project Director to investigators who request it for evaluation of immunodiagnostic, hormonal and enzymatic tests for cancer. The sera collected are adequate to determine the sensitivity and specificity of specific tumor markers and their comparative values with other tumor markers.

Between January 1, 1982 and April 30, 1983 Mayo has collected 59,431 vials from 9,160 patients. They have sent 10 panels of sera to individual investigators during that period of time. The current inventory also includes blood collected from the University of Minnesota and the Philadelphia Geriatric Center, for long-term storage, and is stored in 51 freezers at -75°C .

The availability of multiple serum aliquots on each patient has enabled a multi-institutional NCI collaborative study to be designed using the Serum Bank as a resource. A protocol has been designed consisting of various serum panels to be sent to each of three contractors to perform the prescribed assays. Panels A and B have now been distributed. The study will determine by multivariate discriminant analysis techniques to what extent the simultaneous assay of several unrelated tumor markers will improve the sensitivity and specificity of any of the markers used alone.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 83 Funds: \$199,100

A

CONTACT RESEARCH SUMMARY

Title: Lung Cancer - Early Detection, Localization and Therapy

Principle Investigator:
Performing Organization:

Dr. Myron R. Melamed
Memorial Hospital for Cancer
and Allied Diseases
New York, NY

City and State:

Contract Number: N01-CN-45007

Starting Date: 9/01/73

Expiration Date: 7/31/84

Goal: To evaluate sputum cytology as a supplement to annual chest x-rays in detecting pulmonary neoplasms at an "early stage", to evaluate the efficacy of techniques for prompt localization of radiologically occult lung cancer (e.g., before progression to x-ray positive); and to assess the efficacy of such screening to reduce lung cancer mortality.

Approach: 5,000 test subjects and 5,000 control subjects have been entered into this study. Each subject will receive active screening for at least 5 years, all followed for an additional 5-year period.

Progress: A total of 10,040 men were enrolled into this study. 4,968 were randomly assigned to study group (A), receiving annual chest x-rays and 4-monthly sputum cytology and 5,072 to control group (B), receiving annual x-rays only. There have been a total of 288 confirmed lung cancers identified in the screening period ending in October 1982, 144 in each group. The principal mode of detection in group A was cytology in 27 cases, x-ray in 59 cases and both techniques in 14 cases. Of the 27 cases detected by cytology, 17 were Stage 1; of the 73 cases detected by radiology (or radiology and cytology) in group A and the 88 cases detected by radiology in group B, there were 98 in Stage 1. There were 100 interval cancers diagnosed following symptoms or signs or by x-rays taken outside of the routine screening program; only 19 of these were Stage 1, and 28 were oat cell cancer.

Among the 144 lung cancers appearing in group A, 30 were prevalence cancers for a prevalence rate of 6.0/1,000 and 114 were incidence cancers for an incidence rate of 3.7/1,000/year. In group B, the 144 lung cancers included 23 prevalence for a prevalence rate of 4.6/1,000 and 121 incidence cases, for an incidence rate of 3.8/1,000/year.

The number of lung cancers that were completely resected among the prevalence cases was 29 of 53 (55%); for all the cases it is 151 of 288 (52%). The survival rates are closely related to stage of disease at time of detection and treatment. Adenocarcinoma and epidermoid carcinoma have the best survival; oat cell carcinoma has the poorest survival.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 82 Funds: \$694,978

A

CONTRACT RESEARCH SUMMARY

Title: Use of Multiple Markers in Lung Cancer Diagnosis

Principal Investigator: Dr. Ada R. Wolfson
Performing Organization: Research & Education Institute
UCLA
City and State: Torrance, CA

Contract Number: N01-CB-23929
Starting Date: 9/30/82
Expiration Date: 9/29/84

Goal: To evaluate multiple simultaneous assays of markers in sera of lung cancer patients and to determine by appropriate statistical techniques if there is a combination that will increase both sensitivity and specificity to the point of clinical utility.

Approach: Approximately 1000 frozen coded sera from lung cancer patients, patients with benign disease and normals will be supplied from the NCI Serum Bank for assays on four peptide hormones: lipotropin, calcitonin, alpha glycopeptide subunit chorionic gonadotropin and its β subunit. After receipt of assay data, NCI will supply clinical data for statistical analysis of performance of the four markers. These results will be used in combination with data from other collaborators in this study to ascertain by multiple discriminant analysis techniques if a combination can be found which would be useful for diagnosis and/or prognosis of lung cancer.

Progress: All contractors and biostatisticians in this multi-institutional study met on November 8, 1982 and planned experimental design, quality control and statistical methodology for data analysis. Assay results of lipotropin, calcitonin, alpha glycopeptide subunit chorionic gonadotropin and its β subunit levels on 276 coded sera from the NCI serum bank were reported to the NCI on March 27, 1983. Results of these 4 peptide hormones and 6 other serum markers from other institutions have been supplied to the NCI and combined with clinical data for statistical analysis. The three groups being compared in this serum panel are 95 age and sex matched controls, 95 patients with advanced lung cancer (31 adenocarcinomas, 30 oat cell carcinomas, 34 squamous cell carcinomas) and 79 patients with benign lung tumors or benign lung disease. Biostatisticians at three institutions and the NCI are performing multivariate analysis of the ten serum markers to determine which assays, used in combination, best distinguish patients with advanced lung cancer from controls and patients with benign lung disease.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 83 Funds: \$163,103

A

CONTRACT RESEARCH SUMMARY

Title: Use of Multiple Markers in Lung Cancer Diagnosis

Principal Investigator:
Performing Organization:
City and State:

Dr. Morton K. Schwartz
Sloan-Kettering Institute
New York, NY

Contract Number: N01-CB-23915
Starting Date: 9/30/82

Expiration Date: 9/29/84

Goal: To evaluate multiple simultaneous assays of markers in sera of lung cancer patients and to determine by appropriate statistical techniques if there is a combination that will increase both sensitivity and specificity to the point of clinical utility.

Approach: Approximately 1000 frozen coded sera from lung cancer patients, patients with benign disease and normals will be supplied from the NCI Serum Bank for assays on lipid-bound sialic acid, total sialic acid, ferritin, β_2 -microglobulin and nucleosides and bases. After receipt of assay data, NCI will supply clinical data for statistical analysis of performance of the five markers. These results will be used in combination with data from other collaborators in this study to ascertain by multiple discriminant analysis techniques if a combination can be found which would be useful for diagnosis and/or prognosis of lung cancer.

Progress: A planning session of all contractors and biostatisticians in this multi-institutional study was held on November 8, 1982 to discuss experimental protocol and quality control and to expound on the statistical methodology to be used in analysis of the data. Panel A (276 specimens) was received the first week in January, 1983 and the analyses completed and data reported by March 1, 1983. Biostatisticians at the three institutions involved in this project have now exchanged data and are collaborating with NCI to perform multivariate analyses of the ten serum markers to determine which of these assays in Panel A, used in combination, best distinguish patients with advanced lung cancer from controls and patients with benign lung disease.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 83 Funds: \$135,291

A

CONTRACT RESEARCH SUMMARY

Title: Use of Multiple Markers in Lung Cancer Diagnosis

Principal Investigator: Dr. Leonard Deftos
Performing Organization: University of California,
San Diego
City and State: La Jolla, CA

Contract Number: N01-CB-23930

Starting Date: 9/30/82

Expiration Date: 9/29/84

Goal: To evaluate multiple simultaneous assays of markers in sera of lung cancer patients and to determine by appropriate statistical techniques if there is a combination that will increase both sensitivity and specificity to the point of clinical utility.

Approach: Approximately 1000 frozen coded sera from lung cancer patients, patients with benign disease and normals will be supplied from the NCI Serum Bank for assays on parathyroid hormone (PTH) and calcitonin. After receipt of assay data, NCI will supply clinical data for statistical analysis of performance of the two markers. These results will be used in combination with data from other collaborators in this study to ascertain by multiple discriminant analysis techniques if a combination can be found which would be useful for diagnosis and/or prognosis of lung cancer.

Progress: A planning session of all contractors and biostatisticians in this multi-institutional study was held on November 8, 1982 to discuss experimental protocol and quality control and to expound on the statistical methodology to be used in analysis of the data. Subsequently, the first shipment of samples was received, processed, and assayed for PTH and calcitonin according to established protocols. The results have been forwarded to the NCI and they are undergoing statistical correlation with clinical data. Biostatisticians at the three institutions involved in this project are collaborating with NCI to perform multivariate analysis of the 10 serum markers to determine which of these assays in Panel A used in combination, best distinguish patients with advanced lung cancer from controls and patients with benign lung disease. A similar approach to the second shipment of samples for Panel B is anticipated.

Project Officer: Dr. Bernice T. Radovich
Program: Diagnosis
FY 83 Funds: \$89,314

A

CONTRACT RESEARCH SUMMARY

Title: Statistical Center for Cooperative Lung Cancer Groups

Principal Investigator: Dr. C. Ralph Buncher
Performing Organization: University of Cincinnati
Medical Center
City and State: Cincinnati, OH

Contract Number: N01-CB-43868
Starting Date: 6/10/74 Expiration Date: 2/28/83

Goal: To collect and analyze information from the three clinical centers participating in the lung cancer screening program (directed toward the detection of early lung cancer in high-risk patients) to ascertain the role of this screening program in reducing the mortality and morbidity.

Approach: Procedures have been established with each of the centers and agreement has been reached concerning the common data base for this study. Data are routinely monitored by the Central Statistical Group (CSG), translated into a single computer data base in Cincinnati, and analyzed to provide the combined collaborative information as well as comparative information. Reports are made quarterly. The CSG will continue to search the data from this study for findings which are important and statistically meaningful.

Progress: A common data base for this three clinical center study has been established. Translation and reporting systems for each of the clinical centers have been created and analyses of collaborative results to date have been provided to the NCI and participating clinical centers. Active screening of subjects has been completed at each of the centers. Follow-up information is now being obtained especially to see the pattern of lung cancers that appears after the screening program. Insight into the leadtime, by cell type, will be obtained during the follow-up period. Survival analyses are being generated using the Cox proportional hazard model as well as other models. One-eighth of the 29,735 men have already died. Regular Mortality Review Committee conferences are held to discuss the death certificate and best information cause of death for each man in the study who has died. Mortality comparisons are providing a better understanding of the characteristics of these volunteers for a screening program.

Project Officer: Dr. Bill Bunnag
Program: Diagnosis
FY 83 Funds: \$208,397

A

CONTRACT RESEARCH SUMMARY

Title: Screening Technique for Blood in Stool to Detect Early Cancer of Bowel

Principal Investigator: Dr. Victor A. Gilbertsen
Performing Organization: University of Minnesota Health
Sciences Center
City and State: Minneapolis, MN

Contract Number: N01-CB-53862
Starting Date: 6/30/75

Expiration Date: 12/31/83

Goal: To demonstrate a significant reduction in mortality from colorectal cancer between the screened and the control groups employing the Hemoccult (R) form of the guaiac test for occult blood in the stool in combination with a diagnostic protocol to locate the source of bleeding.

Approach: Forty-five thousand participants between the ages of 50 and 80 years of age with no prior history of colorectal cancer and residing in the state of Minnesota, were randomized into three groups (two experimental, one control) by age, sex and geographic region of the state. Guaiac slides were completed after observance of a meat-free diet with suggested high fiber content and returned to the University by mail, where they were developed in the regular clinical laboratories at the University Hospitals. Groups submitted slides annually and every other year with the third randomized group serving as controls. Each submission consisted of six single well (1 hole for deposit of sample) slides, completed at the rate of two slides from each of three consecutive stools. Participants submitting slides positive for blood receive the diagnostic protocol at the University of Minnesota hospitals and clinics. The protocol includes a complete history and physical examination, upper G.I. series x-ray study (and gastroscopy if indicated) proctoscopy and colonoscopy. Air-contrast Barium Enema X-ray is performed in cases in which colonoscopy does not reach cecum.

Progress: The screening phase of the study was completed December 31, 1982. Follow-up procedures including annual survey to all living participants for the determination of vital status and monitoring of incidence of disease and mortality continues. Epidemiological expertise guides the tracing and determination of vital status on all non-respondents as well as the procurement of certification of death. The Deaths Review Process used throughout the study follows a protocol which includes review of all pathology material, discharge and treatment summaries, hospital and other records relating to the death of a participant, is continued. The panel consists of oncologists, surgeons, the project pathologist, physician-epidemiologist who review the documentation and classify all deaths according to an approved protocol jointly developed by the Principal Investigator and NCI. All cancer deaths receive particular attention for colorectal involvement and all deaths involving colorectal malignancy are classified as from or with colorectal cancer.

Project Officer: Dr. K. Robert McIntire
Program: Diagnosis
FY 83 Funds: \$664,750

A

CONTRACT RESEARCH SUMMARY

Title: Maintain an Animal Holding Facility and Provide Attendant Research Services

Principal Investigator: Ms. Leanne DeNenno
Performing Organization: Bioqual, Inc.
City and State: Rockville, MD

Contract Number: N01-CB-04336
Starting Date: 11/1/79 Expiration Date: 1/10/83

Goal: Maintain colonies of inbred mice (10,000 animals), inbred rats (500 animals), and rabbits (20 animals) and carry out selected breeding protocols with these animals as specified by the project officer. These animals are to be maintained in support of intramural research programs in the Immunology Branch, NCI.

Approach: Colonies of mice, rats, and rabbits are to be housed and fed according to National Research Council standards. Technical manipulations and breeding are to be carried out as directed by the project officer.

Progress: Performance on this contract has been highly satisfactory. The animal colonies have been established and are being maintained according to National Research Council standards. Animal health has, in general, been excellent, and breeding protocols have been satisfactory. Recordkeeping and transferring of animals to and from the NIH Campus have all been satisfactory.

Significance to Cancer Research: This animal colony is necessary in support of intramural research programs in the Immunology Branch of NCI. Many of these programs are concerned with the immune response to cancer.

Project Officer: Dr. David H. Sachs
Program: Immunology Support
Technical Review Group: Ad Hoc Review
FY 83 Funds: \$65,638

B

CONTRACT RESEARCH SUMMARY

Title: Facility for Preparing and Housing Virus Infected Intact and Chimeric Mice

Principal Investigator: Mr. Brian Weatherly
Performing Organization: Bioqual, Inc.
City and State: Rockville, MD

Contract Number: N01-CB-25005
Starting Date: 10/1/82 Expiration Date: 9/30/85

Goal: Perform a variety of in vivo experiments in mice (up to a colony of 3000 animals) that cannot be performed on NIH campus as designated by the Project Officer. These experiments are to be performed in support of intramural research programs in the Immunology Branch, NCI.

Approach: Experiments are to be performed involving the transfer of normal and neoplastic cells, infection with virus, combinations of cells and virus, irradiation with γ -rays or ultraviolet light, preparation of radiation chimeric mice, and transfection with DNA. Protocols and details of experiments are to be carried as directed by the Project Officer.

Progress: Performance of this contract has been very satisfactory. A number of experiments involving virus infection, allogeneic lymphocyte transfer, and combinations of the above have been performed in several mouse strain combinations. The mice have been delivered to Immunology Branch laboratories on schedule as requested, and record keeping of stock mice and experimental protocols have been accurate. The Principal Investigator has ordered mice as requested by the Project Officer. Since the recent installation of the autoclave and the γ -irradiator, radiation chimera experiments have been started. Thus far excellent animal survival has been maintained in the colony.

Significance to Cancer Research: This experimental mouse facility is required to support the intramural research programs of the Immunology Branch of NCI in that it provides research that cannot be performed on the NIH campus due to animal restrictions and use of infectious agents in NIH animal colonies. All of the protocols used in the facility relate to a variety of cancer-related issues including studies on radiation chimeras, induction of tumors, passage of tumors, and development of models of acquired immune deficiency syndrome (AIDS).

Project Officer: Dr. Gene M. Shearer
Program: Immunology Support
Technical Review Group: Intramural Support Contract Subcommittee A
FY 83 Funds: \$266,650.00

B

CONTRACT RESEARCH SUMMARY

Title: Maintain an Animal Holding Facility and Provide Attendant Research Services

Principal Investigator: Ms. Leanne DeNenno
Performing Organization: Bioqual, Inc.
City and State: Rockville, MD

Contract Number: NOI-CB-33876
Starting Date: 1/11/83 Expiration Date: 10/31/87

Goal: Maintain colonies of inbred mice (10,000 animals), inbred rats (500 animals), and rabbits (20 animals) and carry out selected breeding protocols with these animals as specified by the project officer. These animals are to be maintained in support of intramural research programs in the Immunology Branch, NCI.

Approach: Colonies of mice, rats, and rabbits are to be housed and fed according to National Research Council standards. Technical manipulations and breeding are to be carried out as directed by the project officer.

Progress: Performance on this contract has been highly satisfactory. The animal colonies have been established and are being maintained according to National Research Council standards. Animal health has, in general, been excellent, and breeding protocols have been satisfactory. Recordkeeping and transferring of animals to and from the NIH Campus have all been satisfactory.

Significance to Cancer Research: This animal colony is necessary in support of intramural research programs in the Immunology Branch of NCI. Many of these programs are concerned with the immune response to cancer.

Project Officer: Dr. David H. Sachs
Program: Immunology Support
Technical Review Group: Intramural Support Contract Subcommittee A
FY 83 Funds: \$323,382

B

CONTRACT RESEARCH SUMMARY

Title: Characterization of HLA Antigens of Donors' Lymphocytes.

Principal Investigator: Dr. Rene J. Duquesnoy
Performing Organization: Blood Center of Southeastern Wisconsin
City and State: Milwaukee, WI

Contract Number: N01-CB-04337
Starting Date: 6/2/80 Expiration Date: 6/1/83

Goal: To analyze as carefully as possible the cell surface histocompatibility antigens in order to subsequently analyze the relationship between those antigens and the ability of those donors' cells to mount appropriate immune responses.

Approach: Analysis of cell surface antigens is performed by two different detection systems: serology and cellular typing. The serologic analysis is performed using carefully screened alloantisera in assays of complement dependent cytotoxicity. The cellular analysis has been performed by analyzing the proliferative responses to homozygous typing cells (HTC) typing but now is done by analyzing secondary restimulation of lymphocyte populations selectively immunized against alloantigens in primary response (PLT), particularly against antigens of the SB locus.

Progress: As of 5/3/83, approximately 120 samples have been typed in this contract year by serologic techniques for HLA-A, -B, -C, (280 sera/sample) for B cell antigens (140 characterized sera sample and many sera being characterized). There has continuing improvement in the quality and breadth of the sera included on the typing trays. These detailed characterizations of donors HLA regions have supported intramural research projects including: analysis of genetic control of susceptibility to dermatitis herpetiformis; resolution of additional allelic variants of HLA class I molecules; immunogenetic analysis of responses of homosexuals at risk for AIDS (acquired immunodeficiency syndrome); identification of human minor histocompatibility antigens. Expertise in SB typing has been extended, along with the generation of SB-specific primed typing reagents. The first full SB typing was performed on 19 donors using reagents generated both at NIH and by the contractor. There was virtually complete concordance of typing results performed independently at NIH and at the contract facility. As part of the continuing effort of standardization of SB-typing the reference panel of 9 lymphoblastoid cell lines has been sent to an additional 9 laboratories.

Significance to Cancer Research: Evidence from animal models and from epidemiologic studies in humans suggest that host cellular immune responses are crucial in determining the outcome of neoplastic diseases. Cellular immune responses are under control by genes of the major histocompatibility complex (HLA in man). In order to therapeutically manipulate these cellular immune responses, we must first understand their normal operation and genetic control.

Project Officer: Dr. J. Stephen Shaw
Program: Immunology Support
Technical Review Group: Ad Hoc Review
FY 83 Funds: None

B

CONTRACT RESEARCH SUMMARY

Title: Characterization of HLA Antigens of Donors' Lymphocytes

Principal Investigator: Dr. Rene J. Duquesnoy
Performing Organization: Blood Center of Southeastern Wisconsin
City and State: Milwaukee, WI

Contract Number N01-CB-33935
Starting Date 8/1/83 Expiration Date: 7/30/88

Goal: To analyze as carefully as possible the cell surface histocompatibility antigens in order to subsequently analyze the relationship between those antigens and the ability of those donors' cells to mount appropriate immune responses.

Approach: Analysis of cell surface antigens is performed by two different detection systems: serology and cellular typing. The serologic analysis is performed using carefully screened alloantisera in assays of complement dependent cytotoxicity. The cellular analysis is done by analyzing secondary restimulation of lymphocyte populations selectively immunized against allo-antigens in primary response (PLT), particularly against antigens of the SB locus.

Progress: New contract

Significance to Cancer Research: Evidence from animal models and from epidemiologic studies in humans suggest that host cellular immune responses are crucial in determining the outcome of neoplastic diseases. Cellular immune responses are under control by genes of the major histocompatibility complex (HLA in man). In order to therapeutically manipulate these cellular immune responses, we must first understand their normal operation and genetic control.

Project officer: Dr. J. Stephen Shaw
Program: Immunology Support
Technical Review Group: Ad Hoc Review
FY 83 Funds: \$90,378.00

B

CONTRACT RESEARCH SUMMARY

Title: Computer Services

Principal Investigator: Mr. Donald Moore
Name/Address: Department of the Treasury
Performing: 1435 G Street, N.W.
Organization: Washington, D.C. 20220

Contract Number: Y01-CB-90316

Starting Date Nov. 15, 1979

Expiration Date: Sept. 30, 1983

Goal: To provide computer facility for mathematical computations related to biological systems modeling carried out in the Laboratory of Mathematical Biology and other groups in DCBD, NCI.

Approach: Facility is accessed through remote terminals.

Progress: This facility is used only in a backup capacity because our own VAX computer is taking over most of our computations.

Significance to Cancer Research: This facility is used to backup the computational facilities required for continued progress of the Laboratory research programs -- in particular molecular structure and function, membrane structure and function, pharmacokinetics and immunology. All fall within the scope of the National Cancer Plan.

Project Officer: Dr. Charles DeLisi
Program: Cancer Biology Support
Technical Review Group: Ad Hoc Technical Review Group
FY '83 Funds: \$2,000.

B

CONTRACT RESEARCH SUMMARY

Title: Radioimmunoassay and Enzyme Immunoassay of Immunoglobulin Molecules and Antibodies

Principal Investigator: Norman Beaudry
Performing Organization: Hazelton Laboratories, Inc.
Vienna, Virginia

Contract Number: N01-CB1-4344
Starting Date: 6/30/81 Expiration Date: 6/29/84

Goal: To perform radioimmunoassays of immunoglobulin molecules as well as ELISA assays of antibody molecules in lymphocyte culture supernatants or in biological fluids.

Approach: The contractor is to quantitate human IgG, IgA, IgM, IgE, lambda and kappa light chains in various fluids using double antibody radioimmunoassay procedures and reagents defined and supplied by the project officer. Furthermore, the contractor is to measure antibodies produced by lymphocytes stimulated by antigens in vitro. This contract provides critically required research support for the study of immunodeficiencies that are associated with a high incidence of malignancy and on the nature of the malignant transformation that causes human B and T cell leukemias.

Progress: The contract has established radioimmunoassays for IgG, IgA, IgM and lambda and kappa light chains of man and ELISA assays for antibodies. These assays were used to quantitate immunoglobulin and antibody synthesis by human lymphocytes in in vitro cultures. Patients with the adult T cell leukemia associated with human T cell leukemia/lymphoma virus were shown to have a malignant expansion of a suppressor T cell that react with a monoclonal antibody anti-Tac that identifies the inducible receptor for T-cell growth factor, whereas patients with the Sezary syndrome have a malignant expansion of helper T cells that are Tac antigen negative. The assays for immunoglobulin molecules have been an integral part of studies of the arrangement and rearrangement of immunoglobulin genes that are required for a stem cell to mature into a B cell making an immunoglobulin molecule. Furthermore, these assays have been of value in demonstrating that malignancies such as the non-T, non-B cell leukemia of childhood, the hairy cell leukemia and lymphoid blast crisis associated with chronic myelogenous leukemia that previously had been of controversial origin are B-cell precursor leukemias. These studies are defining the nature of disorders of the immune system related to cancer.

Significance to Cancer Research: These studies helped elucidate the abnormalities of the immune system associated with the development of cancer. They have assisted in the categorization of malignancies of the lymphoid system and in the early diagnosis of malignancy and have provided important new insights into the disorder of cell maturation of such malignancies.

Project Officer: Thomas A. Waldmann, M.D.
Program: Cancer Biology Resource
Technical Review Group: Ad Hoc Review
FY83 Funds: \$266,758

A

CONTRACT RESEARCH SUMMARY

Title: Transplantation, Induction, and Preservation of Plasma Cell Tumors in Mice and the Maintenance of Special Strains.

Principal Investigator: Martha J. McGowan, Judith Wax
Lawrence D'Hoostelaere
Performing Organization: Litton Bionetics, Inc.
City and State: Bethesda, MD

Contract Number: N01-CB2-5584
Starting Date: 02-01-82 Expiration Date: 1-31-87

Goal: Induction transplantation, preservation and shipping of plasmacytomas, T- and B-cell lymphomas in mice. Breeding of (congenic) strains of mice, to find genes controlling susceptibility and resistance to the induction of plasma cell tumors by pristane Maintenance of wild mouse colony.

Approach: Maintain a closed conventional colony of inbred and congenic strains of mice, suitable for maintaining mice for long term plasmacytoma induction experiments. Develop BALB/c congenic strains carrying plasmacytoma genesis resistance (PCT-R) genes. Carry out procedures for identifying markers used in the construction of congenic strains. Maintain colonies of pedigreed wild mice. Harvesting and shipment of N₂-frozen transplantable tumors, serum, ascites, tissues, high molecular weight DNA, pedigreed breeders to qualified investigators and collaborators.

Progress: Contractor continues to perform excellently and deliver tumors, inbred and wild mice, and tumor products to the Laboratory of Genetics and other investigators upon request. The tumor reference bank proved invaluable to us by supplying; the Abelson LS, PL and PC tumors. This permitted Dr. Fred Mushinski, et. al., to observe and document the rearrangement of the myb oncogene in PL tumors. The tumor induction studies, preparation of congenic strains has advanced permitting us to make substantial progress in identifying PCT-R genes. The contract has been moved from Kensington to an improved facility in Gaithersburg without interruption. Contractor has improved the wild mouse breeding colony and continues to supply other investigators with reference strains. This colony is probably the only pedigreed source of many of the important representations of the genus Mus.

Significance to Cancer Research: Provides essential support for the study of plasmacytomagenesis (carcinogenesis) with the specific goal of determining the genetic basis of susceptibility to tumor induction by mineral oil. Supplies essential biological material for investigators studying the biology of neoplastic plasma cells, tumor immunology, the genetics of immunoglobulins, and immunoglobulin synthesis.

Project Officer: Dr. Michael Potter
Program: Immunology Support
Technical Review Group: Intramural Support Contract Proposal Review Committee
FY 83 Funds: 616,258

B

CONTRACT RESEARCH SUMMARY

Title: Maintenance and Development of Inbred and Congenic Resistant Mouse Strains

Principal Investigator: Ms. Martha McGowan
Co-Principal Investigator: Mr. J. Scott Arn
Performing Organization: Litton Bionetics, Inc.
City and State: Rockville, MD

Contract Number: N01-CB-25585
Starting Date: 3/1/82 Expiration Date: 1/31/87

Goal: To maintain a colony of inbred pedigreed strains of mice which are needed to support ongoing NCI intramural research in transplantation immunology.

Approach: The contractor maintains a colony of approximately 40 special inbred and congenic resistant strains of mice by pedigreed brother-sister mating. Quality control testing is carried out at each generation by cytotoxicity typing of animals from each strain. Alloantisera are raised between mouse strains to assist in this quality control typing, and sera and animals are shipped by the contractor to collaborating investigators at NIH and elsewhere.

Progress: The contractor has maintained all inbred and congenic resistant strains of mice in excellent condition. Breeding of each strain and of hybrid strains, recordkeeping, and quality control testing have all been highly satisfactory. A backcrossing program has been instituted for all congenic resistant strains in order to keep the backgrounds of these strains identical. This involves backcrossing of each congenic to the reference background line once every 6-10 generations. This program has also been very satisfactory to date. Ten new recombinant H-2 haplotypes have been identified during the process of this backcrossing, and these have been bred to homozygosity and established as new valuable inbred congenic strains.

Hybridoma reagents have been produced, stored and shipped starting with cell lines developed by the Project Officer. Antisera for histocompatibility antigen typing have been prepared in a variety of combinations and have been found to be excellent reagents. A series of new strain-restricted typing sera have been produced in order to identify each strain in the colony and distinguish it from all other strains. Shipping of animals and sera to collaborating investigators at NIH and elsewhere has been very satisfactory. The animals shipped from these pedigreed colonies have generally been of excellent health and have provided breeding stock for the production of larger numbers of experimental animals in numerous laboratories.

Significance to Cancer Research: This animal facility is needed for the breeding and maintenance of these inbred congenic resistant strains of mice. These animals make possible research on individual histocompatibility antigens and, in particular, the role of the major histocompatibility complex in the transplantation of tissues and cells and in the immune response to cancer.

Project Officer: Dr. David H. Sachs
Program: Immunology Support
Technical Review Group: Intramural Support Contract Proposal Review Committee
FY 83 Funds: \$433,963.00

B

CONTRACT RESEARCH SUMMARY

Title: Maintenance of a Feral Mouse Breeding Colony

Principal Investigator: Ms. Martha McGowan

Performing Organization: Litton Bionetics, Inc.
City and State: Rockville, MD

Contract Number: N01-CB-33873

Starting Date: 12-01-82

Expiration Date: 09-30-85

Goal: Induction of mammary tumors with biological (hormones and mouse mammary tumor virus, MMTV) and chemical carcinogens in various feral strains of *Mus musculus* and other species of *Mus*. Breeding of (congenic) strains of feral *Mus musculus* which contain specific genetically transmitted MMTV genomes. Maintenance of a pedigreed feral mouse breeding colony.

Approach: Maintain a closed pedigreed colony of feral mice, suitable for long term mammary tumor induction experiments. Genetically introduce specific endogenous MMTV proviral genomes from inbred mouse strains, into the genetic background of the MMTV-germ line negative *M. musculus* CZII strain. Harvesting and shipment of N₂-frozen primary and transplanted mammary tumors, tissues, and pedigreed feral mice to qualified investigators and collaborators.

Progress: The contractor maintained all of the colonies of feral *Mus musculus* strains and other *Mus* species in excellent condition. The breeding program, records keeping and quality control have all been very satisfactory. Tumor induction studies of MMTV germ line negative *Mus musculus* CZII mice have been initiated using MMTV (C3H) virus and dimethylbenzanthracene (DMBA). CZII congenic mouse strains carrying specific MMTV proviral genomes from Balb/c, C3H, A, and RIIL inbred strains are under development. These studies have led to the identification of the chromosomal location of several genetically transmitted MMTV genomes in inbred mice. Three strains of *Mus cervicolor* *popaeus* have been developed which have a high incidence of mammary tumors many of which are histologically different from those observed in inbred strains of mice.

Significance to Cancer Research: Provides essential support for the study of mammary tumorigenesis with the specific goal of dissecting the genetic and molecular interaction between genetically transmitted MMTV genomes and exogenous carcinogens. Provides essential biological material for other investigators studying the biology of mouse mammary tumor virus as well as other classes of genetically transmitted retroviral genomes.

Project Officer: Dr. Robert Callahan

Program: Immunology Resource

Technical Review Group: DEA; Ad Hoc Intramural Technical Review Group.

FY 83 Funds: \$74,533

B

CONTRACT RESEARCH SUMMARY

Title: Support Services for the Laboratory of Tumor Immunology and Biology

Principle Investigator: Dr. Ronald Gillette

Performing Organization: Meloy Laboratories, Inc.

City and State: Springfield, VA

Contract Number: N01-CP-01018

Starting Date: 11/20/80

Expiration Date: 11/19/84

Goal: To maintain athymic mice bearing human tumor transplants; to prepare large quantities of purified monoclonal immunoglobulins for research and clinical trials; to radiolabel monoclonal antibodies and antibody fragments.

Approach: The contractor houses and maintains athymic mice bearing human tumor transplants for several months; these mice are used in radiolocalization experiments with monoclonal antibodies. The contractor prepares several hundred mg quantities of purified immunoglobulins of each of several monoclonal antibodies; immunoglobulins and their fragments are radiolabeled by the contractor. The contractor also maintains tumor and normal human cell lines.

Progress: The contractor has successfully maintained several hundred athymic mice, each for several months, bearing human breast, colon, and melanoma tumor transplants. These tumors are monitored for time to tumor appearance and tumor size. The contractor has purified to homogeneity several monoclonal immunoglobulins, some of which are to be used for clinical trials. The contractor has successfully maintained numerous human tumor and normal cell lines. The contractor has successfully radiolabeled several monoclonal immunoglobulin and fragment preparations.

Significance to Cancer Research: This contract is necessary for the preparation of purified immunoglobulins to be used in monoclonal antibody research. The radiolabeled immunoglobulins and athymic mouse experiments are necessary preclinical investigations if any of the monoclonal antibodies developed are to be used for localization of tumors in carcinoma patients.

Project Officer: Dr. Jeffrey Schlom

Program: Immunology Support

Technical Review Group: DEA; Intramural Support Contract Proposal
Review Committee

FY 83 Funds: \$480,000

B

CONTRACT RESEARCH SUMMARY

Title: Molecular Biologic Studies of Tumor Viruses

Principal Investigator: Dr. Richard S. Howk
Name/Address: Meloy Laboratories
Performing Organization: Rockville, MD

Contract Number: N01-CB-04342

Starting Date: 6-30-82

Expiration Date: 6-29-83

Goal: To provide support for studies of the structure and expression of tumor viruses.

Approach: Viral biochemical, immunologic, and biological parameters are monitored in different systems to define the regulatory mechanisms of tumor virus expression and to relate the expression to tumor production.

Progress: The contract has been used for support purposes. Plasmid DNAs have been grown in large scale for use in recombinant DNA experiments and for use as probes. This includes plasmids containing p21 viral and cellular ras genes, human papillomavirus DNA segments, Bovine papillomavirus DNA segments, murine retrovirus DNA segments, avian retrovirus DNA segments, and collagen gene segments. Tumors have been grown in animals and used as a source of transformation-related proteins and for the generation of antibodies directed against tumor antigens. Large scale preparations of adenovirus have been made for studies related to the mechanism of virus penetration into cells. Numerous nucleic acid and protein extract preparations have been made from a variety of cells and tissues. These reagents have been used by the investigators for studies outlined in the annual reports of Drs. Lowy and Pastan's laboratories. Immunoperoxidase assays have been performed on many warts in conjunction with a clinical trial of human interferon for the treatment of warts. Immunoblots have also been performed.

Significance for Cancer Research: This research support contract is necessary in support of the intramural research programs in the Dermatology Branch and the Laboratory of Molecular Biology of NCI. Many of these programs are concerned with fundamental mechanisms of carcinogenesis.

Project Officer: Dr. Douglas R. Lowy
Assistant Project Officer: Dr. Ira H. Pastan
Program: Cancer Biology Support
Technical Review Group: Ad Hoc Committee
FY 83 Funds: \$96,000

B

CONTRACT RESEARCH SUMMARY

Title: Hybridoma Assays and Related Laboratory Tests

Principle Investigator: Dr. Ronald Gillette

Performing Organization: Meloy Laboratories, Inc.
City and State: Springfield, VA

Contract Number: N01-CB-33872

Starting Date: 10/1/82

Expiration Date: 9/30/85

Goal: To perform routine immunohistochemistry techniques, and propagate and screen hybridoma cell culture fluids and produce large quantities of hybridoma ascites fluid.

Approach: The contractor maintains a hybridoma production laboratory in which selected hybridomas are cloned and screened for specific monoclonal antibody production. Tissue sections are cut from paraffin embedded and fresh surgical specimens supplied by the project officer; these sections are stained using immunoperoxidase techniques.

Progress: The contractor prepared extracts of human tumor tissue and human tumor cell lines. Hybridoma cell culture supernatants were screened for relevant monoclonal antibody production using solid-phase RIA's. Hybridoma cell lines producing monoclonal antibodies of interest were double cloned and mass quantities of tissue culture supernatants and ascites fluid containing the monoclonal antibodies were prepared. Immunoperoxidase assays and cytospin preparations were performed. Paraffin embedded and cryogenic specimens were sectioned at a 5 micron thickness.

Significance to Cancer Research: This contract is needed to process the large quantity of tissue sections and perform radioimmunoassays needed to screen monoclonal antibodies for specificity. This contract is also needed to produce large quantities of cell culture supernatant fluids and ascites fluids needed for monoclonal antibody research and to supply the numerous laboratories requesting these reagents.

Project Officer: Dr. Jeffrey Schlom

Program: Immunology Support

Technical Review Group: DEA; Intramural Support Contract Proposal
Review Committee

FY 83 Funds: \$216,986

B

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