

A Report to Physicians OncoLog



The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston • July-September 1985 • Volume 30, Number 3

Natural Killer Cells: Research Shows They Are Early Destroyers of Malignancy

Natural killer (NK) cells, whose name comes from their natural ability to destroy tumor cells quickly without deliberate immunization or clonal expansion, are cytotoxic lymphocytes that originate in bone marrow and are present primarily in peripheral blood and lymphoid tissues. Because they may offer important protection against malignancy, Eva Lotzová, PhD, professor of immunology and chief of the MDAH Laboratory of Immunogenetics in the Department of General Surgery, is investigating how to induce or augment them to increase an individual's immunity to cancer.

These cytotoxic lymphocytes deviate from T cells, B cells, and macrophages phenotypically and functionally. They are capable of rapidly killing a wide range of primary and metastatic tumors, both fresh and cultured.

In an interview, Lotzová explained why she believes NK cells, rather than T cells or macrophages, are the first line of defense against malignancy. "NK cells seem to be more important as a first defense because, to mediate antitumor immunity, macrophages need nonspecific stimulation, and T cells, after contact with tumors, must proliferate and form specific tumor-directed clones. This takes several days to a week," she said.

"In addition, T cell surveillance capability is limited because these cells react primarily to tumors that express strong tumor-specific antigens, and these tumors are quite rare. In contrast, NK cells do not require priming, react within 30 minutes to a few hours, and recognize tumors that do not express strong tumor-associated antigens. This argues for a vital role of NK cells in the surveillance system."

To understand how NK cells function, Lotzová stressed that these cells must be seen in the context of the total immune system because their function can be influenced, positively and negatively, by the system's other components. It is known, for instance, that various cell populations produce such biologically active substances as interferon and interleukin-2, which stimulate NK cells.

In 1977 Lotzová and her coworkers were the first to find that NK cells are also regulated negatively by suppressor cells. NK cell-directed suppressor cells were in most systems characterized as macrophages, though T cells were also shown to suppress NK cell activity.

Lotzová believes that the early appearance of NK cells in phylogenetic development and their preservation in higher species, including humans, affirms their basic biologic role as a mechanism of natural immunity. NK cells appear in primitive invertebrates, in whom malignant transformation is rare. This phylogenetic heritage may explain why NK cells perform a basic defense role in recognizing "non-self" structures, defending the host against microbial, viral, parasitic, and fungal infections. Furthermore, in primitive invertebrates as well as in humans, NK cells appear to regulate the growth and differentiation of hemopoietic and lymphoid tissues. Homeostatic regulation and maintenance of the integrity of the organism may be the intrinsic biologic

function of NK cells, according to Lotzová, and may precede their function as defenders against malignant disease.

Morphologically, NK cells are easily identified by a high cytoplasm-to-nucleus ratio, an indented to kidney-shaped nucleus, and azurophilic granules in their cytoplasm. Because of these characteristics, NK cells acquired the designation of large granular lymphocytes (LGLs) (Fig. 1). Even though LGLs have been known for more than 40 years, their cytotoxic powers have been recognized only in the last decade, according to Lotzová. Most NK cells seem to be LGLs, but not all LGLs are necessarily active NK cells.

Absence or Suppression of NK Cells

Just as the NK cells' presence indicates continuing immunosurveillance, their absence or aberrance indicates a weakening of antitumor immunity. Patients with Chédiak-Higashi syndrome, an autosomal recessive disorder, have a high susceptibility to neoplasia, and their LGLs have a morphological defect: a single large cytoplasmic granule replaces the multiple small azurophilic granules present in the normal LGL. This finding of an association between NK cell morphological characteristic and functional defect underscores the importance of recognizing the clues NK cell morphology may offer to diagnosis of clinical immunodeficiency.

Other conditions linked to NK cell deficiency and susceptibility to neoplasia are X-linked lymphoproliferative syndrome, combined immunodeficiency syndrome, systemic lupus erythematosus, paroxysmal nocturnal hemoglobinuria, Sjögren's syndrome, various types of leukemia, and immunodeficiency in allogeneic kidney graft recipients.

Suppression of NK cells also translates into a weakening of antitumor immunity. Experimental animals treated with antibodies directed

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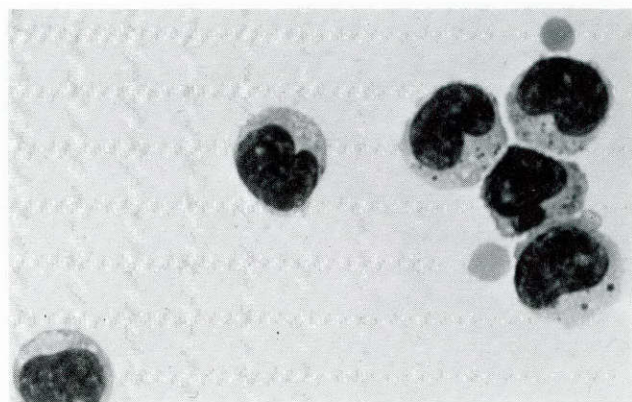


Fig. 1. Large granular lymphocytes have a high cytoplasm-to-nucleus ratio, an indented nucleus, and azurophilic granules in the cytoplasm.

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against NK cells (asialo GM-1 and NK 1.1 antibody) displayed a higher incidence of tumors and lower clearance of tumor cells upon tumor transplantation in vivo. A similar phenomenon was observed by Lotzová's group and other investigators in infant mice that lack active NK cells. Furthermore, such carcinogens as urethane and dimethylbenzanthracene and such tumor promoters as phorbol ester and teleocidin suppress NK cell function and seem to contribute to tumor induction by these agents.

NK Cell Resistance to and Therapy for Leukemia

Lotzová's studies of patients who had acute and chronic myeloid leukemia showed that some had a low frequency of LGLs and others had normal numbers but defects in NK cell lytic mechanisms. These defects included low NK cell cytotoxicity, a low rate of target cell lysis, inability to generate NK cell cytotoxic factor (NKCF), impaired ability to bind to tumors, and virtually no recycling (or renewed capacity) to lyse tumors.

In these patients NK cells were killing, at most, one tumor cell each, whereas normal NK cells kill up to seven tumor cells each. The observation that patients with preleukemic disorders have a similar deficiency in NK cell activity suggests that defective NK cell levels or performance are primary to leukemia. In other words, leukemia seems to be a consequence of low NK cell activity rather than the cause. Leukemia begins in the bone marrow, the site of NK cell origin. Lotzová suggests that once the bone marrow is disturbed, as is the case in patients with preleukemic disorders, NK cell production, differentiation, and influx to blood and other tissues are affected and immunosurveillance is weakened.

"In the light of the NK cells' antileukemic effect," Lotzová said, "we asked whether the NK cell cytotoxic impairment could be corrected in vitro under interleukin-2 stimulation, and we found that NK cell lytic activity was restored within 6 to 21 days in culture. These data demonstrated that the NK cell defect of leukemic patients is a transitory phenomenon, and that the NK cells' tumor-directed cytotoxic potential can be repaired in culture. This strongly suggested that propagation of autologous NK cells of leukemia patients in vitro and their reinfusion in patients may represent a new therapeutic approach to the treatment of leukemia."

Lotzová and a member of her laboratory, C. A. Savary, PhD, currently clone and propagate NK cells from leukemic patients and normal donors to investigate the cells' antitumor potential. The goal is future NK cell therapy for patients with leukemia (Fig. 2).

Lotzová's research provides strong evidence for the role of NK cells in resistance to human leukemia. "The objection to cancer-related laboratory findings," Lotzová said, "has often been that the reactivity of the effector cells—NK cells, T cells, or macrophages—was frequently evaluated against cultured tumors, and such reactivity may not realistically reflect antitumor activity against fresh tumor cells.

"To test whether NK cells were active against fresh human leukemic cells, we used the clonogenic leukemic cell assay, and we were able to show that inhibition of fresh leukemic stem cells was manifested by both allogeneic and autologous NK cells. Our studies, some of them done in collaboration with members of the Division of Medicine, demonstrated that NK cells display resistance against fresh clonogenic leukemic cells—leukemic stem cells—the population of leukemic cells that may be most relevant for expansion of leukemia in vivo," she said.

In other experiments, Lotzová's group studied the cell surface phenotype of NK cells involved in the antileukemic effect using the chronic myelogenous leukemia model and monoclonal antibodies directed against NK cells (Leu-11 and Leu-7) and T cells (Leu-1).

"These studies demonstrated that the leukemia inhibitory activity was abrogated after treatment with Leu-11, and partially with Leu-7 antibody, but not by treatment with Leu-1 antibody, which indicated again that NK cells are involved in this phenomenon," she said.

Studies of the mechanism of NK cell-mediated inhibition of clonogenic leukemic cells showed, furthermore, that NKCF is at least partially responsible for the leukemia-inhibitory effect.

NK Cells and Solid Cancer Therapy

Because of the NK cells' ability to fight tumors, scientists have searched for ways to enhance the cells' antitumor effect. Lotzová and



Eva Lotzová

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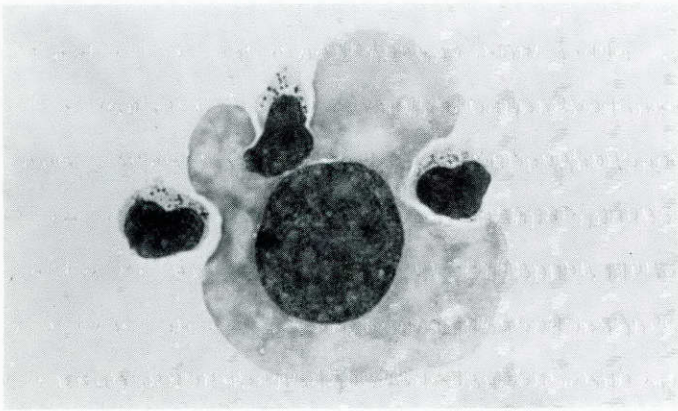


Fig. 2. Three NK cells from a normal donor attack the K-562 cell line, which was derived from a patient with chronic myeloid leukemia in blast crisis. Note multiple granules evident in the NK cells' cytoplasm.

coworkers recently investigated the effect of two new interferon-inducing pyrimidinone molecules—2-amino-5-bromo-6-phenyl-4-pyrimidinol (ABPP) and 2-amino-5-iodo-7-phenyl-4-pyrimidinol (AIPP) on NK cell and antitumor activity. A single intraperitoneal injection of the pyrimidinones (250 mg/kg) resulted in strong induction of NK cell activity in peritoneal exudate, lungs, and liver (tissue expressing low or no NK cell activity) and consistent augmentation of NK cell cytotoxicity against various tumors in the spleen, bone marrow, and peripheral blood of several strains of mice.

“These results are encouraging because they indicate that regional administration of these agents results not only in regional but also in systemic NK cell augmentation. Especially important may be the potentiation of NK cell activity in liver and lungs, the tissues of frequent tumor metastasis. Augmenting NK cells at these sites may diminish metastatic potential,” Lotzová said.

In the next series of experiments, Lotzová and her group used B6D2F₁ hybrid mice to investigate whether NK cell potentiation by AIPP would affect the growth of regionally injected mammary adenocarcinoma ascitic tumor (ACA-755) of B6 origin. Mice were treated with AIPP before or after the tumor cell injection. Control mice invariably died within 17 days. The AIPP-treated mice, however, survived more than four months after the tumor inoculation without any signs of tumor growth.

To determine whether the effect was truly due to the potentiation of NK cells, Lotzová and coworkers treated AIPP-injected mice with NK 1.1 antiserum (which abrogates NK cell activity), with Thy 1.2 antibody (to rule out a T cell effect), and with normal mouse serum as a control. All mice were injected with ACA-755 tumor. Mice that received no AIPP treatment died. All mice treated with AIPP, AIPP and normal mouse serum, or AIPP and anti-Thy 1.2 antibody survived the tumor challenge. Most of the mice treated with AIPP and the NK cell antibody NK 1.1 died from the tumor.

“This experiment showed without any doubt,” Lotzová explained, “that once you stimulate NK cell antitumor immunity and then abrogate the NK cells' action, you no longer have the protective effect. Because the pyrimidinones are powerful stimulators of NK cell activity, they may be particularly important in cancer therapy. Currently, it appears that regional administration of these agents may turn out to be most efficient in cancer therapy.”



Fig. 3. Two natural killer cells bind to ovarian cells.

After studies with the pyrimidinones in mice indicated that regional potentiation of NK cytotoxicity was paralleled by regression of growth of mammary adenocarcinoma, Lotzová's group, in collaboration with Ralph Freedman, MD, Department of Gynecology, and James M. Bowen, PhD, vice president for academic affairs and professor of virology in the Department of Tumor Biology, turned to studying the NK cytotoxic profile of ovarian cancer patients before and after intraperitoneal injection of viral oncolysates (extracts derived from allogeneic cultured ovarian tumor cells whose surface membranes have been modified by the PR-8-A-34 strain of influenza virus) (Fig. 3).

According to Lotzová, ovarian cancer is an excellent model for investigating antitumor immunity in general, because it allows study of the tumor's immunologic profile in situ. Studies of NK cell cytotoxic activity in the peritoneal fluids of ovarian cancer patients showed that the levels of NK cell cytotoxicity were very low, ranging from 0 to 15%. After treatment, NK cell cytotoxicity increased up to 80%, and the NK cell potentiating effect lasted three to four weeks (Fig. 4). The research revealed that the functional NK cell activity in ovarian cancer patients was paralleled by an increase in LGL numbers in the peritoneal fluids and, most important, that the potentiation of NK cell cytotoxic potential was reflected by the regression of malignant ascites. These were completely eradicated in two patients and reduced by 58% to 87% in the other four.

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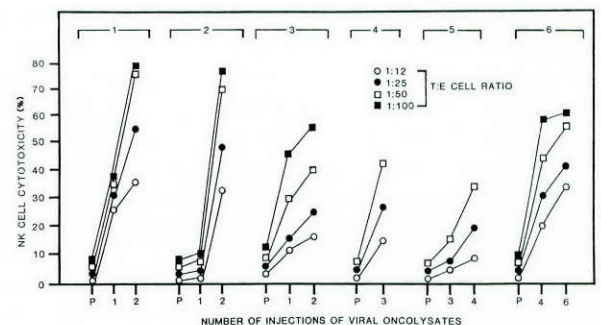


Fig. 4. Injecting viral oncolysates intraperitoneally raised NK cell cytotoxicity from pretreatment levels (P) of 0-15% to as high as 80% in six patients with ovarian cancer. Tumor cell-to-effector cell (T:E) ratios varied from 1:12 to 1:100.

Better Classification and New Drug Regimens Have Advanced Treatment for Lymphoid Cancer

Fernando F. Cabanillas, MD, Department of Hematology, Section of Lymphoma, Division of Medicine, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston

Our ability to classify, diagnose, and treat patients who have a variety of lymphomas has advanced much in recent years. Work in cytogenetics is beginning to clarify the origin of these tumors, and immunobiological research has helped us to understand their behavior. In 1982, an international panel of hematopathologists brought together by the National Cancer Institute proposed a rational classification system of lymphomas. With parallel advances in chemotherapy, we can now treat and cure many patients who have aggressive lymphoid disorders.

Classification

The new working formulation. By the time the nomenclature for lymphoma, devised by Henry Rappaport in 1956 and published by the U.S. Armed Forces Institute of Pathology in 1966, became accepted in our country, it was scientifically obsolete. The main problem was the term "histiocytic lymphoma," which suggested that these tumors were derived from histiocytes. Immunologic studies had already proved that these neoplasms arise from lymphocytes.

The intervening decade brought scores of new classification proposals, all arousing confusion, skepticism, and controversy. As a result, the National Cancer Institute sponsored a multi-institutional study that gave us a new system of nomenclature called the "International Working Formulation." The system blends the salient aspects of previous classifications, such as Rappaport's and Lennert's, and it organizes lymphomas into three histological grades according to tumor aggressiveness and the patients' long-term prognosis. The Working Formulation provides a common language for clinicians and pathologists in different countries and institutions. The new classification with its equivalents in the Rappaport system is shown in Table 1.

New pathological entities. The recognition of two possibly related new entities, peripheral T cell lymphoma and adult T cell lymphoma/leukemia, illustrates the rapid development of this field, thanks mainly to immunologic methods like the use of cell surface markers, which make it possible to distinguish tumors of B cell from those of T cell origin.

The main clinical characteristics of peripheral T cell lymphoma are advanced stage at presentation; frequent "B" symptoms; elevated lactic dehydrogenase (LDH) levels; in varying percentages of patients, involvement of lung or pleura, spleen, or marrow; polyclonal hyperglobulinemia or hypoglobulinemia; and such autoimmune conditions as hemolytic anemia.

Peripheral T cell lymphomas can be subclassified histologically according to lymphoma cell size as diffuse small cell, diffuse mixed, or diffuse large cell lymphomas. In the past, because of histological and clinical similarities, many of these neoplasms were confused with Hodgkin's disease, angioimmunoblastic lymphadenopathy, and immunoblastic sarcoma. The diffuse small cell variant of peripheral T cell lymphoma has been known as Lennert's lymphoma.

Table 1. A Working Formulation of Non-Hodgkin's Lymphomas for Clinical Use and Equivalents in Rappaport Classification

Working Formulation	Rappaport Equivalents
<i>Low Grade</i>	
A. Malignant lymphoma Small lymphocytic consistent with chronic lymphocytic leukemia, plasmacytoid	Diffuse well-differentiated lymphocytic lymphoma
B. Malignant lymphoma, follicular Predominantly small cleaved cell—diffuse areas of sclerosis	Nodular poorly differentiated lymphocytic
C. Malignant lymphoma, follicular Mixed, small cleaved and large cell—diffuse areas of sclerosis	Nodular mixed
<i>Intermediate Grade</i>	
D. Malignant lymphoma, follicular Predominantly large cell—dif- fuse areas of sclerosis	Nodular large cell
E. Malignant lymphoma, diffuse Small cleaved cell—sclerosis	Diffuse poorly differentiated lymphocytic
F. Malignant lymphoma, diffuse Mixed, small and large cell—sclerosis, epithelioid cell component	Diffuse mixed
G. Malignant lymphoma, diffuse Large cell—cleaved cell, noncleaved cell, sclerosis	Diffuse large cell
<i>High Grade</i>	
H. Malignant lymphoma Large cell, immuno- blastic—plasmacytoid, clear cell, polymorphous, epithelioid cell component	Diffuse large cell
I. Malignant lymphoma Lymphoblastic—convoluted cell, nonconvoluted cell	Diffuse poorly differentiated lymphocytic (lymphoblastic)
J. Malignant lymphoma Small noncleaved cell— Burkitt's, follicular areas	Diffuse undifferentiated
<i>Miscellaneous</i>	
Composite	
Mycosis fungoides	
Histiocytic	
Extramedullary plasmacytoma	
Unclassifiable	
Other	



Fernando F. Cabanillas

Today some pathologists believe that most, perhaps all, cases of angioimmunoblastic lymphadenopathy actually represent cases of peripheral T cell lymphoma. Therapy for these disorders has not been highly curative, and it remains to be seen if more modern chemotherapy regimens can extend these patients' survival for longer than the current median of about one year.

Adult T cell leukemia/lymphoma, first described in Japan where the disorder is widespread, represents the other newly identified lymphadenopathic disease. The neoplasm has been linked to the recently described human T cell leukemia virus and appears to be caused by it. The virus was recovered from cultured tumor cells, and its discovery offers hope of identifying other viruses that may cause lymphomas in humans.

Prognostic Factors

Knowledge of pertinent prognostic factors is crucial for planning clinical trials as well as analyzing their results. Several studies of prognostic factors of these heterogeneous tumors have been conducted in the past 10 years. The results of these studies have been similar, although some differences are evident from the summary shown in Table 2. Most of the data are derived from patients with aggressive lymphomas. Some differences arose from the use of different treatment regimens and some from the inclusion of different histological tumor types. Basically, the presence of bulky tumor and elevation of LDH level predict a poorer response. Identifying patients who have these adverse characteristics may lead to innovative therapeutic approaches such as bone marrow

Table 3. Common Karyotypic Abnormalities in B Cell Lymphomas

Cell Type	Common		Variants	
Burkitt's	t(8;14)	(q24;q32)	t(8;22) t(2;8)	(q24;q11) (p13;q24)
Follicular ("nodular")	t(14;18)	(q32;q21)	t(7;14) t(8;14)	(q23;q32) (q22;q32)
Diffuse large cell	del (6) + 7 + 12	(q21)	t(8;14) t(14;18) + 3	(q24;q32) (q32;q21) + 10

transplantation, an intervention still too risky to be used except as a last resort.

Chromosomal Abnormalities

The introduction of the banding technique in cytogenetics has made it clear that many chromosomal abnormalities in leukemia and lymphoma are consistent and not random. Some of these abnormalities are translocations, and deletions and extra chromosomes also occur frequently. Table 3 is a summary of the common karyotypic abnormalities of these lymphomas. Much knowledge remains to be gained in distinguishing, or classifying correctly, the correlations of chromosomal abnormality and lymphoma type.

Management

Stages I and II aggressive lymphomas. Although most patients with lymphoma present with advanced stage III or IV disease, some present with earlier-stage disease. Considerable controversy exists about the best therapy for these patients, particularly for those whose tumors are classified in the Working Formulation as intermediate and high-grade aggressive. Whether surgical staging is necessary and whether chemotherapy alone, radiotherapy alone, or a combination of the two offers the best results have been the central questions.

One complication is that the median age of patients with lymphoma other than Hodgkin's disease is 55 years. Consequently, elective surgical staging is often contraindicated in at least a third of

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Table 2. Major Prognostic Factors That Predict Complete Response in Lymphoma

Investigators*	Treatment	Diagnosis	Bulkiness	LDH	Marrow Involvement	Prior Rx	Age	Sex	B Symptoms
Koziner	CTX-L ₂ & NHL-3	DHL	NA	++	+	+	+	-	-
Cabanillas	COP	ALL	++	NA	-	+	-	+	-
Fisher	CVP, CMOPP, BACOP, XRT	DHL, DUL	++	+	++	-	-	-	++
Velasquez	CHOP-BLEO	DHL	++	++	-	NA	++	-	-

Abbreviations: CTX-L₂, cyclophosphamide-L₂; NHL-3, non-Hodgkin's lymphoma stage 3; DHL, diffuse histiocytic lymphoma; NA, not analyzed; COP, cyclophosphamide, vincristine (Oncovin), prednisone; ALL, acute lymphoblastic leukemia; CVP, cyclophosphamide, vincristine, prednisone; CMOPP, cyclophosphamide, methotrexate, Oncovin, procarbazine, prednisone; DUL, diffuse undifferentiated lymphoma; BACOP, bleomycin, doxorubicin (Adriamycin), cyclophosphamide, Oncovin, prednisone; XRT, X-ray therapy; CHOP-BLEO, cyclophosphamide, doxorubicin, Oncovin, prednisone, bleomycin.

***Investigators:** Koziner et al., *Cancer* 49:1571-1579, 1982; Cabanillas et al., *Arch. Intern. Med.* 138:413-418, 1978; Fisher et al., *Blood* 58:45-51, 1981; Velasquez et al., *Proceedings of the American Society of Clinical Oncology* 3:244, 1984, abstract C-954.

Rural Science Park is Laboratory for Basic Work on Carcinogenesis

Describing the fundamental investigations at the UT System Cancer Center's Science Park-Research Division at Smithville as "research in cancer cause and prevention" is accurate, but it's a summary, not an explanation.

Earlier this year, the 200-page grant application reviewing the division's research activities resulted in a \$1 million five-year award from the American Cancer Society. As a result of the large grant, the researchers will now be able to conduct studies of the influence of nutrition and dietary habits on the etiology of neoplastic diseases, in addition to enlarging the staff and buying some costly laboratory equipment.

The goal of more than 100 staff members in the "think tank" environment in Bastrop County is to advance understanding of the three basic processes of cancer: cell damage, change, and proliferation as a result of genetic or environmental influences. Closest neighbors to benefit from this knowledge will be the clinicians and patients at UT MDAH but, obviously, the benefits will be worldwide.

Research at Science Park, directed by Thomas J. Slaga, PhD, and associate director Earl F. Walborg, PhD, is supported by many other grants and nonstate funds totaling slightly more than \$3 million per year and by state funds of nearly \$1 million a year.



Wooded path in Science Park.

"We are rapidly becoming one of the premier carcinogenesis research centers in the world," Slaga said.

Cancer Causation

Currently, studies of the causes of cancer include investigations of the critical cellular and molecular targets of chemically induced carcinogenesis in several models, including the skin, vagina, liver, and tracheobronchial tree of rodents. The researchers are attempting to clarify carcinogenic stages and to identify the cellular processes in tumor formation.

Because one biological consequence of DNA damage is malignant disease, the scientists are analyzing DNA changes that occur when animals or cells in culture are exposed to carcinogenic agents. Cell survival and mutation are being studied, as are the reactions of cells known to have good or poor DNA repair capacity.

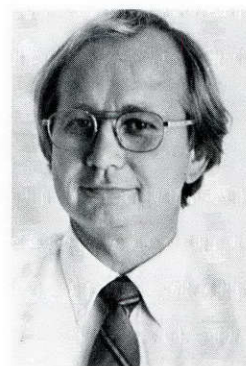
Although the viral origin of thyroid tumors in leukemic mice is known, the role of viral chromosomal sequences in chemical- or radiation-induced formation of lymphomas remains to be determined. Science Park researchers are using lymphoma-prone mice to study the role of recombinational genetic events and altered viral proteins in leukemia in these animals.

Work with hybrid fish is yielding information about the role of specific gene loci of a heritable melanoma, and a study of the normal growth and differentiation of stem cells—embryonic cells in skin, blood, and other systems—is intended to reveal early carcinogenic events during the evolution of these cells.

Preventing Cancer Induction

Animal tumor models—mouse skin, rat liver, rat respiratory system, and mouse vagina—are providing Science Park researchers with information about the inhibition of cancer formation. If nontoxic inhibitors—such as antioxidants, some vitamins, protease and polyamine inhibitors, selenium, interferon, steroids, and hormonelike compounds—prove active in some of the models tested, the work may lead to a rational approach to cancer prevention in human beings.

The study of skin cancer prevention shows, for example, that some of these nontoxic compounds inhibit formation of skin tumors at different stages of cell development. It may be possible, therefore, to coun-



Thomas J. Slaga

The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston

DIAGNOSIS AND TREATMENT STRATEGIES FOR GYNECOLOGIC CANCER

The Twenty-ninth Annual Clinical Conference on Cancer and the Eighteenth Annual Special Pathology Conference

November 13-16, 1985 Shamrock Hilton Hotel Houston, Texas

The primary goals of the 1985 clinical conference are to present current knowledge on the diagnosis and treatment of gynecologic cancer and to highlight areas that are both controversial and important to the practicing physician. The conference will include presentations on the more common endometrial, cervical, and ovarian cancers but will also address developing areas such as the use of biologic response modifiers and tumor markers in therapy.

ACCOMMODATIONS

A block of rooms is reserved for registrants at the Shamrock Hilton Hotel, South Main and Holcombe, Houston, Texas. Early hotel registration is suggested. Please mention the M. D. Anderson clinical conference in any contacts with the hotel to be assured of receiving the special meeting rates of \$68 per night single or double occupancy. The hotel phone number is (713) 668-9211.

Any questions or correspondence concerning this conference should be directed to:

1985 Clinical Conference
Office of Conference Services, HMB Box 131
UT M. D. Anderson Hospital and Tumor Institute
6723 Bertner
Houston, Texas 77030
Phone: (713) 792-2222



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 - Friday
 - Saturday
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 - \$175 registration fee enclosed (M. D. Anderson associate members)
 - Will pay on arrival (\$250 onsite)
 - Exempt

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teract carcinogenesis with very low doses of a combination of antioxidants, protease inhibitors, and an inhibitor of the enzyme ornithine decarboxylase, difluoromethylornithine (DFMO).

Interferon, DFMO, and antioxidants in various combinations seem to inhibit mutagenesis and carcinogenesis in mouse skin and liver. Selenium and beta-carotene may prove to be tumor inhibitors in a model that employs allogeneic mouse liver transplants. Hormonal compounds, because of their relation to oral contraceptives, are being tested for both tumor induction and tumor inhibition in mouse vagina, and the possible halting of morphogenesis and tumor progression of bronchial carcinoma is studied in *in vitro* as well as *in vivo* models that include transplanted tissue.

The influence of dietary life-style and nutrition on cancer is next on the Science Park program because many studies have shown that nutrients and other dietary components may alter the incidence of tumors in a variety of epithelial tissues, including skin, lung, bladder, breast, pancreas, colon, and liver.

This new program, funded by the American Cancer Society, will focus on the mechanisms by which dietary fat contributes to cancer induction in the mammary gland, large bowel, or pancreas.

"The new project," Slaga said, "will add a new dimension to our research activities as well as advance our current work."

Science Park researchers come from many different disciplines, and they collaborate with scientists at UT MDAH, The University of Texas at Austin, and Texas A&M University. They contribute to undergraduate training at nearby Southwest Texas State University at San Marcos, Southwestern University at Georgetown, and Trinity University at San Antonio. Graduate fellows come from UT-Austin, Texas A&M, and the Graduate School of Biomedical Sciences of the UT Health Science Center at Houston. [OncoLog](#)

(Physicians who desire more information may write Thomas J. Slaga, PhD, director, Science Park-Research Division, The University of Texas System Cancer Center, P.O. Box 389, Smithville, Texas 78957—ED.)

Natural Killer . . .

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To be certain that the antitumor effect was caused by NK cells, Lotzová and her associates used NK cell-specific Leu-11 antibody and complement to treat the effector cell population. This treatment abolished NK cell activity directed against malignant ascites in both normal donors and ovarian cancer patients and confirmed the NK cells' role in reactivity to these types of tumors. In addition, Lotzová demonstrated that incubating malignant ascites with NK cells resulted in production of NKCF, which on its own (without NK cells) was effective in killing malignant ovarian cells. The studies with ovarian cancer patients thus showed that NK cell potentiation or adoptive transfer of NK cells or NKCF may represent a viable therapy for ovarian cancer.

Applications

"I do not believe that I am overly optimistic in suggesting that the information on NK cells, which we and other investigators are providing, could result in vital therapy for certain patients with leukemia, ovarian cancer, and perhaps also with other types of malignancies," Lotzová said. She believes that cloning propagation of NK cells *in vitro* may lead to new protocols for cancer treatment, and that such treat-

ments as NK cell transfusion or infusion of NKCF will be a part of NK cell protocols in future therapies.

"We can propagate NK cells *in vitro*. They grow well and retain their cytotoxic function for several months, which indicates that this approach is technically feasible. Animal experimental studies have demonstrated that such *in vitro* cloned NK cells are effective in mediating tumor resistance," she said.

NK cells also have been shown to be effective in fighting infections, she said, so that further work should allow potentiation of the antimicrobial resistance of patients receiving chemotherapy. In addition, Lotzová and others have shown that NK cells are involved in rejection of allogeneic bone marrow transplants. NK cells may therefore have prognostic value in the selection of donor-recipient pairs for bone marrow transplantation. [OncoLog](#)

(Physicians who desire additional information may write Eva Lotzová, PhD, Laboratory of Immunogenetics, Department of General Surgery, MDAH Box 41, The University of Texas M. D. Anderson Hospital and Tumor Institute, 6723 Bertner Avenue, Houston, Texas 77030—ED.)

Better Classification . . .

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these patients, either because of age or associated medical problems. Furthermore, these aggressive tumors may progress in a short time. Up to 20% of patients in some series have developed progressive disease either soon after surgical intervention or during radiotherapy. That is why we believe it is better to use clinical rather than surgical staging, but this also means that we will fail to identify a small percentage of patients who have subclinical stages III or IV disease.

We and others have used combination chemotherapy that resulted in an 80% to 86% relapse-free survival of patients at two years and 80% to 100% overall survival at two years. These data have to be interpreted carefully, however, because patients with early-stage aggressive lymphomas seem to be more prone to late relapse than patients with more advanced lymphomas. Usually, however, second remissions are relatively easy to attain in cases of late relapse.

Our current policy is to use clinical staging followed immediately by chemotherapy with doxorubicin-based regimens, followed by radiotherapy later to consolidate treatment gains. The role of radiotherapy is still not totally clear, but it is likely to help prevent local relapse, especially in patients who have bulky tumors. Use of clinical staging followed only by radiotherapy has been abandoned by most investigators because of poor results.

Stages III and IV aggressive lymphomas. The single most important factor in predicting whether or not patients with lymphoma can be cured is the quality of their therapeutic response. Complete response (CR) becomes progressively difficult for patients at higher lymphoma stages.

The first effective treatments for patients with aggressive lymphomas were limited by the small number of active drugs available. Thus, if a patient achieved only a partial remission after being treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), not much else could be done.

Two recently introduced regimens have consisted of such new drugs as ifosfamide and etoposide (VP-16-213), as well as high-dose metho-

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trexate. Using sequential chemotherapy regimens and late intensification, we have been able to achieve a complete response in 46 of 56 patients who have aggressive lymphomas. Our CR rate for patients with disease in stages I through III was 100%, and 66% for those in stage IV. We schedule the treatment regimens according to response to therapy, changing to the next regimen whenever a patient achieves a less than complete response after three courses of CHOP. The next regimen is doxorubicin, cytarabine, prednisone, and bleomycin (HOAP-BLEO), and the next is ifosfamide, methotrexate, and etoposide (IMVP-16). Compared with previous experience with doxorubicin-based chemotherapy, the multiregimen approach not only yields a higher CR rate but also results in longer survival.

Refractory or recurrent lymphomas. In our trials and those of others, several single agents have shown activity in patients with recurrent lymphomas, including etoposide (21% response rate in 116 patients), ifosfamide (47% in 15 patients), mitoguazone (37% in 63 patients), and amsacrine (14% in 50 patients). In our most recent trial we used mitoguazone, ifosfamide, methotrexate, and etoposide in a combination regimen called MIME. The analysis of the results of this regimen is based on a regression model that predicts response rate based on these pretreatment prognostic factors: quality of the patient's response to first-line therapy, diagnosis (indolent versus aggressive lymphoma), and central nervous system involvement.

Among 208 patients treated with MIME, the overall response rate was 60%, and the CR rate was 24%. Patients with aggressive lymphomas had a somewhat higher response rate: 64% overall and 32% CR. Patients with indolent lymphomas in this group had a 54% overall response rate and 12% CR.

When we applied the regression model prospectively to the MIME-treated patients, we found an overall expected response rate of 53%, compared with the observed response rate of 60%, a significant difference. Major improvements occurred mainly in patients who had indolent lymphomas and whose predicted probability of response was lowest. We believe their improvement may be attributed to the inclusion of mitoguazone, a drug with substantial activity in these tumor types.

The median relapse-free survival of 15 months for the complete responders to MIME has been identical to previous experience with IMVP-16 and the amsacrine, ifosfamide, etoposide combination. About 20% to 30% of complete responders have maintained their response

beyond two years, which suggests that they may be cured of lymphoma.

Other approaches to management of patients with recurrent lymphomas include megadose chemotherapy with or without radiotherapy and rescue by either autologous or allogeneic marrow transplantation. From one study, it appears that Burkitt's lymphoma is especially amenable to autologous bone marrow transplantation because of the tumor's sensitivity to alkylating agents. The heterogeneity of the lymphomas and the limited experience with bone marrow transplantation make interpretation of these studies difficult.

Further work with combined chemotherapy regimens and bone marrow transplantation will have to be done. But, meanwhile, the classification of the lymphomas has made treatment trials both more logical and successful, and it has improved our ability to evaluate our own and others' attempts to treat and cure these patients. [OncoLog](#)

(Physicians who desire additional information may write Fernando F. Cabanillas, MD, Department of Hematology, MDAH Box 77, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, 6723 Bertner Avenue, Houston, Texas 77030—ED.)

New Book: Candidiasis

Candidiasis, edited by Gerald P. Bodey, Sr, MD, and Victor Fainstein, MD, both of the Department of Internal Medicine, Section of Infectious Diseases, reviews current understanding of the pathogenesis, manifestations, diagnosis, treatment, and prevention of superficial and systemic candida infections.

Published by Raven Press (1985, \$45.50, 281 pages, 54 illustrations), the book has 23 contributors from medical centers throughout the country, whose research and treatment reports emphasize candida infections in cancer and acquired immune deficiency syndrome patients and in patients whose host defense mechanisms have been altered by therapy. Therapies discussed include those with broad-spectrum antibiotics, adrenal corticosteroids, cancer chemotherapeutic agents, immunosuppressants used in organ transplantation, and intravenous hyperalimentation.

Because the number of immunocompromised patients continues to increase, *Candidiasis* will be of special interest to infectious disease specialists, immunologists, and other clinicians who treat patients at risk for candida infections. [OncoLog](#)