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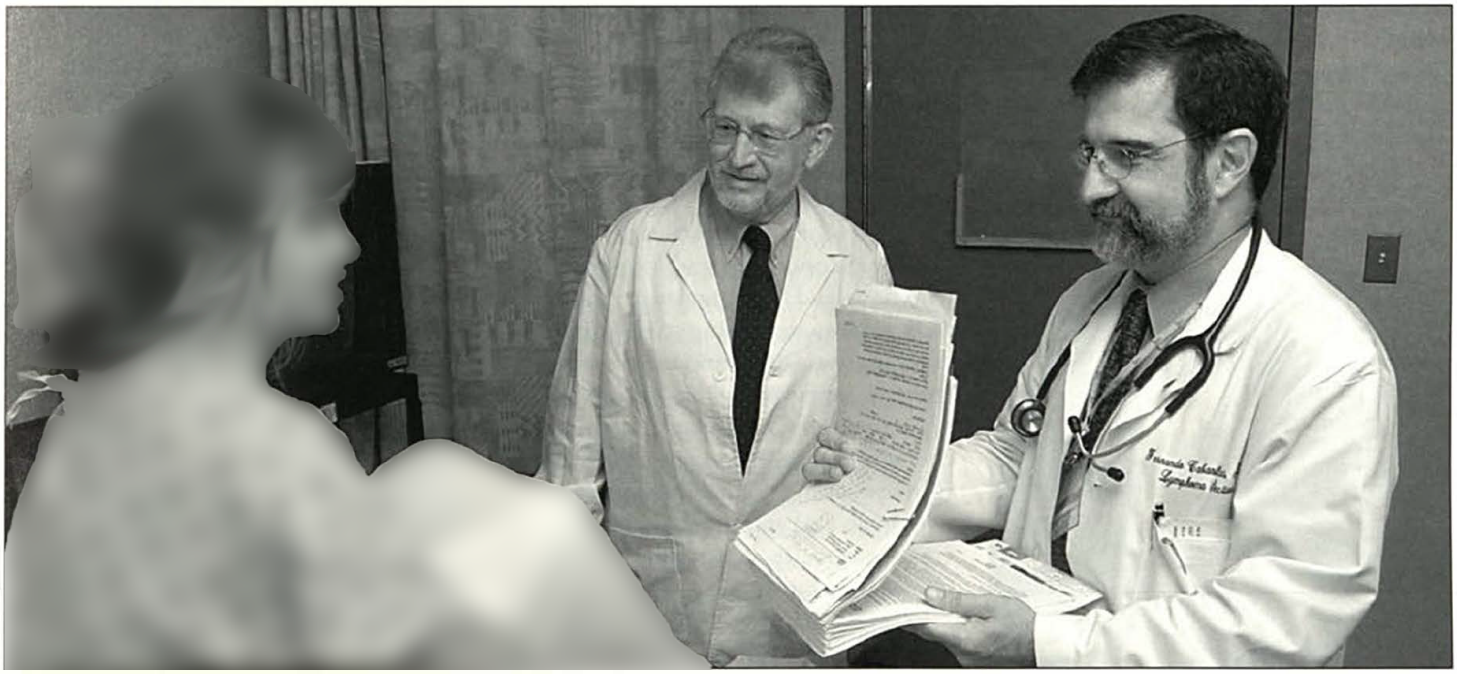
Researchers Focus on Bioimmunotherapy for Treatment of Non-Hodgkin's Lymphomas



by Beth Notzon

The sheer number of non-Hodgkin's lymphomas—about 30 in all—has always presented a complex challenge to researchers. Whether they are indolent and grow slowly, like follicular lymphoma, or are aggressive, fast-growing tumors such as Burkitt's lymphoma, all are serious cancers. Now the incidence of non-Hodgkin's lymphoma, already the fifth most common cancer in the United States, is on the rise and so is the pressure on researchers to develop better treatments and more sensitive diagnostic techniques for this diverse group of tumors.

(Continued on **next page**)

[redacted] *who came to M. D. Anderson from* [redacted]*, speaks with* **Dr. Fernando Cabanillas** *(right), chairman of the Department of Lymphoma and Myeloma, as* **Dr. Javier Garcia-Conde**, *a visiting physician from Spain, looks on. Researchers at M. D. Anderson are investigating molecular therapies to treat patients with non-Hodgkin's lymphomas.*

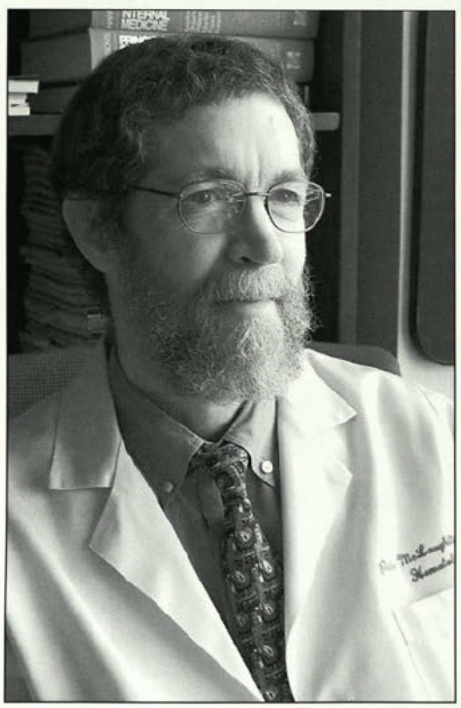
THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Bioimmunotherapy for Non-Hodgkin's Lymphomas

(Continued from **page 1***)*

In part because lymphomas are derived from lymphocytes, which are part of the immune system, these tumors are particularly good candidates for treatment with bioimmunotherapy, said Fernando Cabanillas, M.D., chairman of the Department of Lymphoma and Myeloma at The University of Texas M. D. Anderson Cancer Center.

Rituximab, one of the first success stories in bioimmunotherapy for cancer, is being studied further in clinical trials of patients with indolent B-cell lymphomas, which constitute 40% of the cases of non-Hodgkin's lymphoma. Despite the usually slow growth of these tumors, the long-term mortality rate is high because the tumors often become resistant to current standard treatments. Peter McLaughlin, M.D., a professor in the Department of Lymphoma and Myeloma who has headed up much of the research on rituximab at M. D. Anderson, explained that rituximab is an unconjugated anti-CD20 monoclonal antibody that recognizes and disrupts the activity of CD20, a transmembrane protein found normally on B cells but also expressed on most B-cell lymphomas. Antibodies against CD20 have proven to be effective targeted therapies, both in an unconjugated form (rituximab) and when linked to radioisotopes to deliver targeted radiotherapy (Zevalin). The role of CD20 in normal B cell biology and in the development and progression of B-cell lymphomas remains incompletely understood and is the focus of much current research.



Dr. Peter McLaughlin, *a professor in the Department of Lymphoma and Myeloma, has been studying rituximab, a monoclonal antibody against the cell-surface protein CD20, for the treatment of B-cell lymphomas.*

Researchers in the Department of Lymphoma and Myeloma at M. D. Anderson led a large multicenter clinical trial of rituximab that concluded in 1996. In this study, in which rituximab was used alone, a response rate as high as 69% was seen in certain groups of patients. A particular advantage of rituximab is that it seldom causes serious side effects. This is especially good news for elderly patients with comorbid conditions and for patients who have had bone marrow transplants. Now rituximab is being studied in combination with standard chemotherapy regimens and has shown a synergistic effect with certain chemotherapeutic agents. A new clinical trial is investigating the combination of rituximab and epratuzamab, an anti-CD22 monoclonal antibody, without chemotherapy.

Zevalin, another anti-CD20 antibody, is being studied for use in radioimmunotherapy. In this treatment, the antibody attaches to CD20 on the cancer cell and delivers a radioisotope, yttrium 90, which has a long-range effect, killing tumor cells up to a few millimeters away from the target tumor cell. This treatment is efficacious when a large amount of the radioisotope is delivered by the antibody to the tumor, said Franklin C. Wong, M.D., Ph.D., J.D., an associate professor in the departments of Nuclear Medicine and Neuro-Oncology. Dr. Cabanillas pointed out that a particularly intriguing mechanism of this therapy is that the radioisotope can destroy not only the tumor cells with CD20 but also, through a "cross fire" effect, nearby tumor cells that do not have the antigen. Zevalin is approved for use in patients with recurrent indolent B-cell lymphoma, including those with disease resistant to rituximab. Clinical studies of the therapeutic effects of radioiodinated antibody against CD20 in patients with lymphoma are also under way at M. D. Anderson and other institutions.

Another cell-surface protein that holds promise as a target for the treatment of lymphomas is CD26, which is the focus of preclinical research being conducted by Nam Hoang Dang, M.D., Ph.D., an assistant professor in the Department of Lymphoma and Myeloma. This work extends previous findings by Dr. Dang in collaboration with Chikao Morimoto, M.D., a research professor in the department, that demonstrate a key role for CD26 in normal T lymphocyte function. CD26 is involved in the development of T-cell lymphoma, a very aggressive type of non-Hodgkin's lymphoma. Most T-cell lymphomas are so aggressive, in fact, that patients with the disease are expected to live only a few months to a year with current treatment. Dr. Dang explained that most patients with T-cell lymphoma have disease in the bone marrow, lymph nodes, and other sites at the time of diagnosis. Adding to this bleak picture is the fact that T-cell lymphomas are very refractory to current treatments. Thus, a critical need exists for better treatments for this type of lymphoma.

In laboratory studies, early indications are that the antibody to CD26 inhibits the growth of T-cell lymphomas, at least in mice. Like rituximab, the antibody to CD26 may augment the effectiveness of other therapies, either by making cells more sensitive to chemotherapy or by reducing the number of cancer cells the chemotherapy has to destroy. CD26 itself may also sensitize lymphomas to certain types of chemotherapy by affecting certain cellular processes in the tumor

cells. Additional studies are being performed to translate these laboratory findings to animal models, with potential implications for the treatment of patients with T-cell lymphomas as well as other lymphomas. Taking advantage of what is known about CD26 biology, Dr. Dang has initiated a clinical trial evaluating the effect of chemotherapy on CD26 expression in tumor cells and in normal T lymphocytes.

Researchers at M. D. Anderson have also been developing a quantitative technique that is sensitive enough to determine whether a patient with follicular lymphoma is in molecular remission—that is, if the number of tumor cells has become so low that the cancer can no longer be detected. Andreas H. Sarris, M.D., Ph.D., a former member of the Department of Lymphoma and Myeloma, and Yunfang Jiang, M.D., Ph.D., a research scientist in the department, began using quantitative polymerase chain reaction to test for molecular remission, and the technique is now the focus of research being done by Andre Goy, M.D., an assistant professor in the department. Dr. Cabanillas explained that the test can detect one abnormal cell out of 100,000 normal cells on the basis of a certain genetic abnormality. The particular strength of this test resides in its potential ability to help clinicians decide whether to increase a patient's dosage or change the treatment—or whether to consider the patient potentially cured.

"The data show that, without a doubt, patients who achieve a molecular remission have a much longer period of remission. If they have minimal residual disease, however, they will have a relapse within two years," said Dr. Cabanillas.

At an even more basic scientific level, researchers are looking for the causes of non-Hodgkin's lymphoma and trying to identify the molecular mechanisms involved. In one such effort, Felipe Samaniego, M.D., an assistant professor in the department, is identifying how human herpesvirus 8 may cause primary effusion lymphoma.

In part because lymphomas are derived from lymphocytes, which are part of the immune system, these tumors are particularly good candidates for treatment with bioimmunotherapy.

(For more details, please see DiaLog on page 8.) Although a viral etiology for non-Hodgkin's lymphoma remains more suspected than proven, this may be the first real evidence that a virus can cause lymphoma.

Other molecular research is being conducted in Dr. Goy's laboratory, where the molecular profile of diffuse large cell lymphoma tumors is being studied in vivo to define a subset of genes that could help predict the tumor's response to chemotherapy.

"This is a very exciting project that is part of our broader efforts to define the genes important in the progression and prognosis of lymphomas," Dr. Goy said.

A discussion of bioimmunotherapy would not be complete without a look at a vaccine being tested in patients with indolent non-Hodgkin's lymphoma. A particular problem with advanced indolent lymphoma, as Dr. Cabanillas explained, is that "although the tumor is very slow growing, the patients' chances of cure are very low." The most likely reason for the ineffectiveness of current standard treatments for this type of lymphoma is that they preferentially target rapidly cycling cell populations. Because cells in the slow-growing types of non-Hodgkin's lymphoma divide slowly, the chemotherapy simply cannot find its target. A tumor vaccine being tested by Anas Younes, M.D., an associate professor in the Department of Lymphoma and Myeloma, may overcome some of the problems seen with standard therapies. The vaccine, which is called HSPPC-96, is made using a cancerous lymph node removed from the patient being treated. Dr. Younes explained that of the nine patients enrolled so far in a phase II trial of HSPPC-96, none has shown any major side effects, and two have shown a response.

Generally, tumor vaccines differ from vaccines for such diseases as polio and smallpox in that, first of all, they are being used to treat, not to prevent, the cancer, and second, they are made specifically for a particular patient. Dr. Younes explained that this is necessary because, although different patients can have the same type of lymphoma, one patient might have a tumor that makes five antigens, whereas another patient's tumor might produce 200 antigens. Therefore, a vaccine that works in the first patient would not work in the second patient. Dr. Younes noted that if results from the phase II trial are encouraging, the vaccine will be tested in patients with indolent lymphomas who are in complete remission to see if it can prolong the duration of remission or increase the cure rate.

More than 25 years ago, members of the Department of Lymphoma and Myeloma conducted the work that led to the landmark development of the CHOP regimen (cyclophosphamide, hydroxydaunomycin, Oncovin [vincristine], and prednisone) for non-Hodgkin's disease. More recently, they developed the now-standard and very effective FND regimen (fludarabine, Novantrone [mitoxantrone], and dexamethasone), as well as a number of other regimens used as salvage therapy. This legacy of innovation lives on as researchers cast a wide net in their search for ways to improve the prospects of patients with lymphoma. ●

FOR MORE INFORMATION, *contact Dr. Cabanillas at (713) 792-2860, Dr. McLaughlin at (713) 792-2860, Dr. Wong at (713) 794-4649, Dr. Dang at (713) 745-3130, Dr. Goy at (713) 792-2860, Dr. Samaniego at (713) 792-2860, or Dr. Younes at (713) 792-2860.*

See page 4 for Protocols.

Non-Hodgkin's Lymphoma Studies

Clinical trials in progress at The University of Texas M. D. Anderson Cancer Center include the following for patients with relapsed or refractory non-Hodgkin's lymphomas.

INDOLENT LYMPHOMA
Conventional-Dose Therapy

Combination therapy with biological agent

- Fludarabine, mitoxantrone, and dexamethasone (FND) plus rituximab for relapsed or refractory low-grade lymphoma (DM00-081). *Physician: Fredrick B. Hagemeister, M.D.*

Single agents

- Phase II study of irinotecan for the treatment of relapsed or refractory non-Hodgkin's lymphoma (DM97-182). *Physician: Andre Goy, M.D.*
- Phase II study of 506U78 for patients with indolent or peripheral T-cell lymphoma previously treated with chemotherapy (ID99-208). *Physician: Andre Goy, M.D.*
- A phase II study of oxaliplatin in relapsed and refractory non-Hodgkin's lymphoma (ID99-406). *Physician: Anas Younes, M.D.*

Biological agents

- A phase II study of recombinant human interleukin-12 for the treatment of relapsed lymphoma and Hodgkin's disease (DM97-073). *Physician: Anas Younes, M.D.*
- A phase II trial of active specific immunotherapy in patients with indolent lymphoma using autologous lymphoma-derived heat shock protein-peptide complex (ID99-354). *Physician: Anas Younes, M.D.*
- A phase II, open-label, randomized multicenter trial of Hu1D10 in patients with relapsed or refractory grade I, II, or III B-cell non-Hodgkin's lymphoma (DM01-397). *Physician: Luis E. Fayad, M.D.*

Radiotherapy/radiolabeling

- Salvage of chemotherapy failure with central lymphatic irradiation for follicular lymphoma (ID98-309). *Physician: Chul Soo Ha, M.D.*
- A multicenter, open-label trial to evaluate the efficacy and safety of IDEC-Y2B8 (Zevalin) radioimmunotherapy of relapsed or refractory low-grade or follicular transformed B-cell lymphoma (DM99-398). *Physician: James Lee Murray, M.D.*

AGGRESSIVE LYMPHOMA
Conventional-Dose Therapy

Combination therapy

- A phase I trial of BBR 2778 in combination with cytarabine, methylprednisolone, and cisplatin in the treatment of patients with relapsed or refractory aggressive non-Hodgkin's lymphoma (DM01-398). *Physician: Luis E. Fayad, M.D.*
- A phase II study of paclitaxel and topotecan with filgrastim-SD/01 support for patients with relapsed and refractory aggressive non-Hodgkin's lymphoma (DM01-008). *Physician: Anas Younes, M.D.*

Single agents

- DM97-182 (see above)
- ID99-406 (see above)
- Pivotal phase II multicenter study of vincristine sulfate liposome injection in aggressive non-Hodgkin's lymphoma that is refractory or relapsed after second-line combination chemotherapy (DM00-009). *Physician: Alma Rodriguez, M.D.*

Biological agents

- DM97-073 (see above)
- DM01-397 (see above)

Radiotherapy/radiolabeling

- DM99-398 (see above)
- Phase I study of 1311-Lym-1 for the treatment of previously treated diffuse large B-cell lymphoma (ID00-195). *Physician: James Lee Murray, M.D.*

FOR MORE INFORMATION *about these clinical trials or for a complete listing of clinical trials for patients with non-Hodgkin's lymphoma, call the M. D. Anderson Information Line. Those within the United States should call (800) 392-1611; those in Houston or outside the United States should call (713) 792-6161. Visit the M. D. Anderson clinical trials Web site at www.clinicaltrials.org for a broader listing of treatment research protocols.*

Research Consor
Role of Genetics

by Karen Stuyck

Within the past 16 years, scientists have identified approximately 50 different genes that predispose people to cancer. While the most well-known inherited cancers are probably breast and ovarian cancers associated with mutations of the BRCA1 or BRCA2 gene, "genes are being linked to the development of every tumor type from kidney cancer, colon cancer, and certain endocrine cancers to melanoma and nonmelanoma skin cancers," said Louise Strong, M.D., a professor in the Section of Clinical Cancer Genetics at The University of Texas M. D. Anderson Cancer Center.

To help researchers learn more about how genes affect the development of cancer and how information about genetic susceptibility can best be integrated into patient care, the Texas Cancer Genetics Consortium is recruiting people at high risk of cancer who might be willing to participate in research studies. Funded by the National Cancer Institute in 1998, the Texas Cancer Genetics Consortium is part of the nationwide Cancer Genetics Network. M. D. Anderson is the coordinating institution for the consortium, and the other participating institutions are Baylor College of Medicine, The University of Texas Health Science Center at San Antonio, and The University of Texas Southwestern Medical Center at Dallas. While the Texas group is focusing on individuals at high risk, other network institutions are recruiting volunteers from the general

tium Recruiting Volunteers to Study the in Cancer Development and Patient Care

Karen Copeland, *the senior genetic counselor in the Clinical Cancer Genetics Program at M. D. Anderson, explains how genetic traits are passed on in families. Copeland counsels participants in the Texas Cancer Genetics Consortium, which is part of a nationwide effort led by the National Cancer Institute to learn more about genetic susceptibility to cancer and how best to integrate that knowledge into patient care.*

population for their studies.

So far the Texas network has recruited about 850 individuals who are at high risk for the development of inherited cancers, according to Karen Copeland, the senior genetic counselor in M. D. Anderson's Clinical Cancer Genetics Program and a former consortium coordinator and genetic counselor at The University of Texas Health Science Center at San Antonio.

Dr. Strong, who is the principal investigator of the Texas research consortium, said that the group hopes to recruit many more people who have a strong family history of cancer (a single type of cancer or multiple cancers within the family) or who have had multiple primary cancers or cancer at an unusually early age. "Our goal is to develop an extensive resource of patients with cancer, survivors, and family members to serve as study participants," said Dr. Strong.

Network participants receive free newsletters with the latest information about genetic susceptibility to cancer and have the opportunity to take part in research studies, Dr. Strong said. That research may be aimed at primary prevention, chemoprevention, early detection, or education about inherited cancers, or it may involve more basic research.

"Many people who are at high risk are very eager to follow any new approaches to early detection and prevention," Dr. Strong said. Participating in the research consortium's studies allows them to take advantage of these new options. As for the basic research studies, "Most people who have an inherited predisposition to cancer are very anxious that the body of knowledge about this continues to grow. Obviously, they have hope that we'll have better information to offer and better options for their children and descendants than we may have had for them or their parents," she said.

Most consortium participants are recruited through a genetic counseling and testing facility in their area. Once someone joins the network, he or she completes a questionnaire focusing on personal and family history of cancer. Some of the information from the questionnaire is sent to the national network—with no identifiers and without revealing the participant's name—and entered into a computer database. Initially, participants might only complete the questionnaire, or they might also decide to take part in research studies. They also agree to be contacted about future research studies.

"We can offer network participants genetic testing, counsel them about their cancer risk, offer them recommendations for management, and let them know about any new information on their particular condition," Dr. Strong said.

Most cancers result from random genetic mutations that occur because a mistake is made when cells are dividing or in response to injuries from environmental agents such as radiation or chemicals. Inherited cancers, however, develop in part from mutations carried in reproductive cells. These mutations are passed on from one generation to the next and are present in cells throughout the body. People who inherit cancer are more likely to develop the disease at a young age.

Genetic counselors assess the likelihood that the cancer in the participant's family is hereditary and talk about genetic testing, said Copeland. Evaluating the patient's risk starts with constructing a two- or three-generation family pedigree. "Based on that, we have a pretty good idea whether the cancer is hereditary," she said.

About half of the people Copeland counsels are reassured to learn that the cancer in their family is not inherited. If a person does have a family history of hereditary cancer, Copeland discusses the implications with the individual and helps them make an informed decision about whether to proceed with genetic testing.

"Only 5% to 10% of all cancers are hereditary," Copeland said. "This includes about 8% to 10% of colon cancers, 5% to 7% of breast and ovarian cancers, and less than 1% of cervical and lung cancers."

Genetic tests are not available for all cancers. Some of the most common genetic tests, said Copeland, detect a person's predisposition to inherited breast and ovarian cancers and to two

(Continued on **page 6***)*

Research Consortium to Study Role of Genetics

(*Continued from* **page 5**)

types of inherited colon cancer, hereditary nonpolyposis colon cancer (HNPCC) and familial adenomatous polyposis (FAP).

Because of variations in mutations and gene alterations, some genetic tests can more accurately predict risk than others. In the BRCA1 and BRCA2 tests for inherited breast and ovarian cancers, about 80% of the women who have gene alterations will be identified. The HNPCC test identifies about 60% to 70% of people with genetic mutations, Copeland said, while the FAP test pinpoints 90% to 95% of the cases because there is less variability in FAP mutations.

About 50% to 60% of the consortium participants who are eligible for genetic testing choose to have it. After the testing, patients return for counseling to discuss the results. If a genetic susceptibility for cancer is found, a physician specializing in that type of cancer may participate in the session, helping the patient to understand the diagnosis and discussing risk reduction and screening recommendations. If a medical specialist is not at the session, the patient is referred to an appropriate physician. If needed, Copeland can also refer the patient to a psychotherapist.

There is now much that can be done for people identified as being at high risk for cancer, Dr. Strong said. Preventive surgery, such as prophylactic mastectomy or oophorectomy, can reduce a person's risk of breast or ovarian cancer by 90%. Others may choose to avoid the risks and morbidity associated with major surgery and opt for increased surveillance. They may decide, for instance, to participate in a cancer genetics network study on early detection of ovarian cancer in women at high risk, which involves having blood tests every three months and ultrasonography every six months. In addition, an early-detection study for breast cancer is in the planning stages.

Chemoprevention trials are another option for some patients at high risk. Dr. Strong cited several studies of chemoprevention of inherited colon cancer as well as the Study of Tamoxifen and Raloxifene (STAR), a breast cancer prevention study comparing the safety and efficacy of the two drugs.

Dr. Louise Strong, *a professor in the Section of Clinical Cancer Genetics, is the principal investigator of the Texas Cancer Genetics Consortium. The consortium aims to recruit patients at high risk of cancer into research studies.*

While familial cancers are rare, studying them has important implications for learning about other, more common, cancers. Cancer cells, in general, have more genetic alterations than normal cells.

"It turns out that the genes that predispose to cancer and are altered in rare inherited cancers are generally also altered in the more common, nonhereditary tumors. In the hereditary cases, the alterations are present in all tissues, which greatly increases the probability of cancer by increasing the chance of additional genetic changes. In the nonhereditary cases, the genetic alterations are present only in the tumor, not in the normal tissues, and are acquired in the development of the tumor," Dr. Strong said. "So we have learned enormous amounts about the biology of cancer through identification of these rare cancer-susceptibility genes. Studying these relatively rare heritable syndromes has been extremely informative in beginning to understand what makes a cancer cell different from a normal cell."

Since 1978, Dr. Strong has been studying Li-Fraumeni syndrome, a rare heritable condition that increases susceptibility to many different kinds of cancer through mutations in the p53 gene. "It's one gene alteration that puts one at high risk of cancer but with a very unpredictable age of onset or cancer site," she said. While mutated p53 is rarely inherited, p53 is "the most commonly mutated gene in human cancers in terms of the accidental, acquired kinds of mutations," Dr. Strong said. "It's a key player in cancer development."

To enroll in the Texas Cancer Genetics Consortium, individuals or their physicians may call (877) 900-8894 or the M. D. Anderson Clinical Cancer Genetics Program office at (713) 745-7391 (e-mail, ccg@mdanderson.org).

"Right now we probably have more information on inheritable breast, ovarian, and colon cancers and more research studies going on in those groups, so we're especially interested in recruiting people with those conditions. But we can offer resources for people at high risk of other inheritable cancers as well," said Dr. Strong.

Current research studies that network members may participate in include trials of ovarian cancer screening among women at high risk, familial prostate cancer, modifiers of risk in women at high risk of breast cancer, and sibling pairs with colon cancer.

Dr. Strong would also like to increase the diversity of network participants. "We hope to have a better presence in the minority community. These genes affect all ethnic and socioeconomic groups, and it's important that everybody has the opportunity to be informed and to participate," she said. ●

HOUSE•CALL

The First Cancer Prevention Vaccine

You may think that by eating healthy foods, not smoking, and maintaining a healthy weight, you are doing all you can to prevent cancer. But did you know that 5% of the cases of hepatocellular carcinoma, a type of liver cancer, are caused by the hepatitis B virus? Did you know that hepatitis B infection is preventable through vaccination? It is, effectively, the first cancer prevention vaccine.

Hepatocellular carcinoma is serious. According to the American Cancer Society, more and more people with liver cancer are dying from it, a trend that is unlike those in many other cancers. Right now, only 10% of patients with liver cancer live for at least five years after diagnosis. Each year, up to 320,000 Americans are infected with hepatitis B, and 1,500 die from liver cancer associated with the infection. All could be prevented by the widely available, safe, and effective vaccine against contracting hepatitis B.

What is the connection between hepatitis B and liver cancer? The hepatitis B virus damages the DNA of liver cells, making the liver more prone to developing cancer. These damaged liver cells may be damaged further while carrying out the regular detoxifying function of the liver. This cumulative damage can lead to the cells developing into tumors.

While most adults completely recover from hepatitis B infection, 90% of infants, 30% of children, and 10% of adults with hepatitis B become chronically infected, according to the Centers for Disease Control and Prevention (CDC). Chronic infection means that the hepatitis B virus is always active in the body and signals a greater chance of liver damage that can lead to liver cancer. However, even if someone fully recovers from hepatitis B infection, liver damage that could lead to liver cancer may have already occurred. As many as half the people infected with hepatitis B never experience any symptoms.

Hepatitis B is spread from person to person through contaminated blood transfusions, by sharing needles or having sexual contact with an infected person, through ear and body piercing, tattooing, or acupuncture treatments with contaminated equipment, and from an infected mother to her infant at birth. The American Liver Foundation advises against sharing toothbrushes and razors. Hepatitis B is not spread through food, water, or casual contact. This means that certain groups of people are at high risk for hepatitis B infection. The Hepatitis B Foundation describes these groups as sexually active adults and teenagers; health, dental, and emergency care personnel; families adopting children from regions of the world with a high prevalence of hepatitis B infection; intravenous drug users; and people who live with hepatitis B carriers.

The hepatitis B vaccine, which prevents hepatitis B viral infection throughout a person's lifetime, is administered in a series of three intramuscular injections, given one at a time over a period of six months. You cannot contract hepatitis B from the vaccine, and the most common side effects are swelling and soreness at the injection site. You can receive the vaccine from your doctor or public health clinic. The CDC recommends hepatitis B vaccination for all infants. The Hepatitis B Foundation recommends additionally that all school-age children, adolescents, and college students who have not already been vaccinated receive the vaccine. Recently, the U.S. Food and Drug Administration approved a new combination vaccine that protects against both hepatitis A and B.

Each year, up to 320,000 Americans are infected with hepatitis B, and 1,500 die from liver cancer associated with the infection.

All could be prevented by the widely available, safe, and effective vaccine against contracting hepatitis B.

The world over, hepatitis B is the leading cause of liver cancer. A simple, safe vaccine could prevent you from ever having to wonder or worry about hepatitis B infection. Why not add vaccination against hepatitis B to the choices you make to prevent cancer? ●

For more information, contact your physician or contact the M. D. Anderson Information Line:

(800) 392-1611 *within the United States, or*

(713) 792-6161 *in Houston and outside the United States.*

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The Viral Origins of Lymphomas

Felipe Samaniego, M.D.
Assistant Professor, Department of Lymphoma and Myeloma

Almost half of all lymphomas contain one or more viruses that have been linked to the development of the disease. For example, Epstein-Barr virus is present in non-Hodgkin's lymphoma and Hodgkin's disease tumors, and human herpesvirus 8 (HHV-8) is found in all primary effusion lymphomas. In rare cases, HHV-8 infection alone is believed to be sufficient to transform lymphocytes and cause lymphomas. This makes HHV-8–infected lymphocytes a good model for the study of lymphoma development.

The vast majority of individuals who become infected with these viruses experience clinical symptoms only at the time of initial infection, and then the virus becomes dormant. However, in individuals with immune deficiency and, rarely, in those with apparently normal immunity, signs of virus gene expression and replication in susceptible lymphocytes become evident, and over time lymphoma develops.

Lymphocytes have evolved several antiviral defenses that restrain viral spread. To combat infection, cells use their innate properties to detect infection and induce cell suicide, thus depriving the virus of the cell's reproductive machinery. To counteract cell suicide, viruses have in turn developed genes that block apoptosis. For example, the HHV-8 genome contains a homologue of the human bcl-2 oncogene, and as with human bcl-2, its expression effectively blocks cell apoptosis. Presumably, viral bcl-2 operates in vivo to sustain cell survival at critical times for the virus, allowing it to complete the cycle of replication and infection. This effect, which was originally designed to help the virus survive, can also enhance the actions of other viral genes and collectively promote cell immortalization and eventual transformation into cancer.

The HHV-8 genome also contains homologues of other human genes: a viral IL-6 gene whose expression mimics human IL-6 in stimulation of cell proliferation; a viral macrophage inflammatory protein that modulates replication of viruses; and a novel receptor-like gene called K1 that structurally resembles immune cell receptors. In cell culture, K1 expression blocks Fas signaling and prevents apoptosis of lymphocytes.

Viruses have also developed ways to avoid detection by immune system cells. Infected lymphocytes send out alarm signals that use B-cell receptors attached to their cell surface. When the K1 gene of HHV-8 is expressed in a lymphocyte, normal assembly of the B-cell receptor is prevented, lymphocyte communication is paralyzed, and the lymphocyte remains infected and possibly undetected.

Though specifically designed to preserve the cycles of virus replication and infection, the collateral effect of HHV-8's selective blockade of the signaling underlying apoptosis and lymphocyte immune response is to immortalize the lymphocyte and transform it into lymphoma.

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