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OncoLog

Translational Research Speeds the Journey from Lab Results to Clinical Outcomes

by Beth Notzon

While basic science researchers work to unravel the mysteries of the causes of cancer and the cellular and molecular mechanisms involved, clinical researchers study the effects of new drugs and other treatments on patients with cancer. For decades, efforts have been under way to bring the two ends of the research spectrum together to translate the findings in the laboratory into increasingly more effective cancer treatments. In recent years, this collaborative spirit has become so much a part of the cancer research climate that translational research is now a byword of cancer research.

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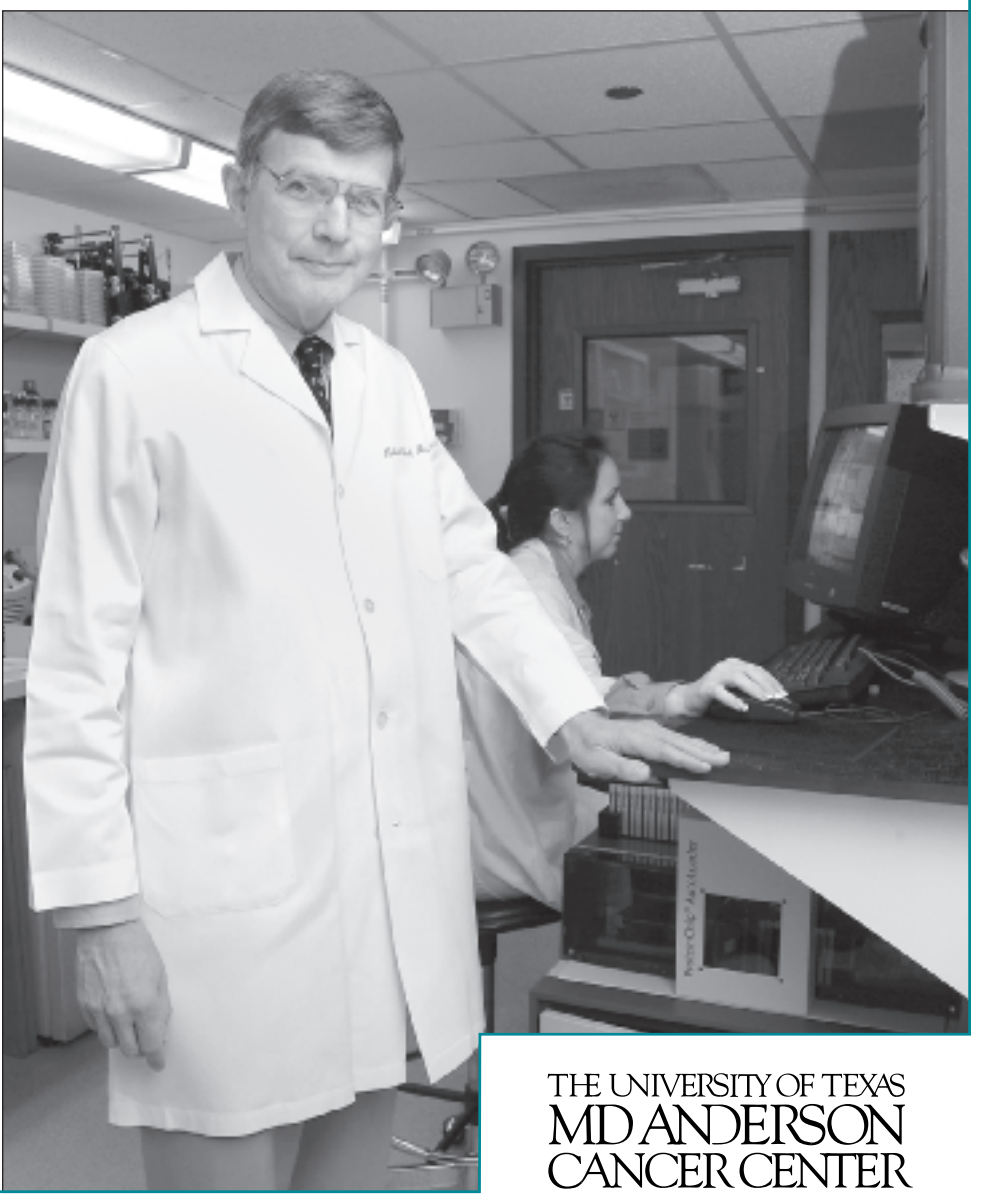

Dr. Robert C. Bast, Jr., *vice president of the Office of Translational Research, oversees all translational research conducted at M. D. Anderson.*

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Translational Research Speeds the Journey

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"Translational research is really about trying to bring together the progress we're making in the laboratory with the progress we're making in the clinic." This is how Robert C. Bast, Jr., M.D., vice president of the Office of Translational Research at The University of Texas M. D. Anderson Cancer Center, sums up the current situation in cancer research. "If you look at the progress that has occurred in the laboratory in the past 10 to 20 years, our knowledge has increased exponentially. Our progress in the clinic—in detecting, preventing, and curing cancer—has increased steadily but is more linear, more incremental."

M. D. Anderson's Office of Translational Research was created in 2000, with Dr. Bast as its first head. This office has as its chief responsibility coordinating and facilitating translational research conducted at M. D. Anderson and collaborating institutions—in effect making sure that the right hand always knows what the left hand is doing.

Dr. Bast is a veritable directory of the translational research being done at M. D. Anderson, and he can provide a litany of names and research areas. In some cases, very basic research can have an impact on important clinical problems. For example, Benoit deCrombrugghe, M.D., identifies genes that control bone formation and destruction, which are especially relevant to breast and prostate cancers that metastasize to bone. Studies of basic tumor immunology also are leading to new treatments for cancer. Several years ago, Eugenie Kleinerman, M.D., translated observations of immunostimulants in a mouse model into a novel and effective treatment for osteosarcoma in children. Yong Jun Liu, M.D., Ph.D., an authority on antigen-presenting cells, recently arrived at M. D. Anderson and is working to develop vaccines for cancer. Jeffrey J. Molldrem, M.D., has already developed some of the first effective vaccines for leukemia, and cancer vaccines are also the focus of Patrick Hwu, M.D., and Larry Kwak, M.D., Ph.D., who are building a remarkable community of researchers whose goal is to translate immunologic insights into clinical results.

Antiangiogenesis is a primary research interest of Isaiah J. Fidler, Ph.D., D.V.M. The aim of antiangiogenic research is to block tumor growth by starving it of blood-borne nutrients. Michael O'Reilly, M.D., and Lee M. Ellis, M.D., also work with laboratory models to understand angiogenesis and to develop novel methods for inhibiting tumor growth. James L. Abbruzzese, M.D., Roy Herbst, M.D., Ph.D., and Christopher Logothetis, M.D., have translated laboratory observations into novel clinical trials of angiogenesis inhibitors, alone and in combination with cytotoxic drugs. Renata Pasqualini, Ph.D., and Wadih Arap, M.D., Ph.D., are studying molecular "zip codes" on the inner surface of tumor-associated blood vessels that might be used to deliver drugs and other agents selectively to cancers. At the same time, researchers such as Edward F. Jackson, Ph.D., and John D. Hazle, Ph.D., are working out ways to measure angiogenesis using diagnostic imaging methods, initially in animal models and subsequently in patients. A recent addition, Juri Gelovani, M.D., Ph.D., is developing a molecular imaging method that can identify biochemical changes in cancers before and after treatment.

Dr. Edward F. Jackson, *an associate professor in the Department of Imaging Physics, examines magnetic resonance data in a new high-field (3-Tesla) magnetic resonance suite. Dr. Jackson is developing ways to noninvasively monitor microvascular changes using magnetic resonance imaging methods.*

Gene therapy is the focus of research for a large group at M. D. Anderson that includes Michael Andreeff, M.D., Ph.D., Jack A. Roth, M.D., Gary Clayman, M.D., and Mien-Chie Hung, Ph.D. Other investigators, such as Jean-Pierre Issa, M.D., are devising ways to reawaken the expression of silenced genes that can inhibit cancer growth.

In cancer prevention, Scott M. Lippman, M.D., and his colleagues are testing several different drugs to protect people against prostate, breast, and colon cancer. Over the years, Waun Ki Hong, M.D., and Reuben Lotan, Ph.D., have been at the forefront internationally in the study of retinoids to prevent tobacco-initiated cancers. Molecular epidemiologists, led by Margaret Spitz, M.D., are identifying methods to assess the risk of developing cancer, and researchers such as Xifeng Wu, M.D., Ph.D., are making exciting discoveries in the area of single-nucleotide polymorphisms, which offer promise as a way to identify people in large popula-

tions at risk for certain cancers who would benefit from cancer screening and chemoprevention.

As these research interests illustrate, translational research occurs at each organ site. Dr. Bast himself heads up the ovarian cancer Specialized Programs of Research Excellence (SPORE) grant, and he noted that SPORE grants are "specifically translational research grants." Or, as the National Cancer Institute Web site explains, the main purpose of these grants is "to promote interdisciplinary research and to speed the bi-directional exchange between basic and clinical science to move basic research findings from the laboratory to applied settings involving patients and populations." Eight other SPORE grants awarded to M. D. Anderson are in the areas of lung, head and neck, endometrial, bladder, pancreatic, and prostate cancer; melanoma; and leukemia.

Another byword in cancer research is targeted therapy. Translational research is particularly feasible now because of, as Dr. Bast explained, "the new understanding of what causes cancer in different individuals, which relates to different combinations of genetic events." This understanding has come primarily from the work of basic research scientists. Until fairly recently, the only effective way to treat cancer was to destroy or eliminate the cancerous cell using surgery, radiation therapy, and chemotherapy. These treatments destroy not only cancerous cells but also healthy cells, leading to the often serious side effects that are a hallmark of most traditional cancer treatments. While these standard therapies will continue to play an important role in the treatment of patients with cancer, they can be vastly aided in this process by targeted therapy, which literally targets the aberrant biochemical pathways that actually cause the cancer. Malignant cells become dependent on only a few abnormal chemical signals for their survival. Normal cells have many different biochemical pathways that ensure their survival. Therefore, targeting only one pathway in malignant cells leaves normal cells unharmed. Gordon Mills, M.D., Ph.D., has found that inhibition of the PI3 kinase enzyme can selectively kill ovarian cancer cells, with tolerable toxicity to normal cells, particularly when the inhibitor is used in combination with a standard cytotoxic drug such as paclitaxel. This approach promises to open up an entirely new vista in cancer treatment. As Dr. Bast explained with some excitement, "It is now possible to imagine designing a specific prescription for each patient wherein you would

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Translational Research Speeds the Journey

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treat just exactly those abnormalities that occurred in their cancer."

It may take a while for this particular dream to become a reality, but in the meantime, translational research is already making an important difference in the lives of cancer patients. A prime example of this is imatinib mesylate (Gleevec), a drug that has shown amazing promise in the treatment of patients with chronic myelogenous leukemia (CML). "This is the poster child of translational research," Dr. Bast noted. The development of the drug began with the finding that 99% of patients with CML have a single type of molecular abnormality in their white blood cells—a chromosomal translocation that results in the formation of an aberrant Bcr-Abl fusion protein that constantly activates Abl kinase, which is ordinarily only intermittently activated. The continuous activation of the enzyme causes CML cells to proliferate and survive.

"Ninety-eight percent of patients in the chronic phase of CML respond initially to Gleevec. About a third of the patients will show a resolution in molecular abnormalities. And it is even possible to effectively treat patients who lapse into blast crisis," Dr. Bast said. These results improve dramatically the outlook for most patients with CML.

According to Dr. Bast, translational research is focusing on "identifying new drugs, antibodies, or genes that would either neutralize the oncogenes, the 'accelerators' that turn on tumor growth, or that would replace the 'brakes' on cell growth, the dysfunctional tumor suppressor genes. Targeted therapy can also intervene in the signaling pathways of cancer cells so that the cancer cells would be stimulated to self-destruct, whereas normal tissues would be spared."

He went on to explain that translational research is not just a single process. "You are talking about the whole spectrum of cancer research," Dr. Bast said. "There is translational research at all different sites—breast cancer, gastrointestinal cancer, lung cancer, and prostate cancer. There is also translational research in early detection, diagnosis, prevention, and treatment."

> ***"Translational research is really about trying to bring together the progress we're making in the laboratory with the progress we're making in the clinic."***
>
> **– Robert C. Bast, Jr., M.D., vice president, Office of Translational Research**

Moreover, the process of translational research is not a one-way street. Discoveries also travel from the clinic to the laboratory in the form of clinical observations, human tissue, diagnostic images, and blood samples, which researchers use to further unlock the secrets of cancer. Prime examples of this are studies of the cells from patients with CML who have become resistant to Gleevec, such as those being led at M. D. Anderson by Moshe Talpaz, M.D. Stanley Hamilton, M.D., has developed a molecular monitoring laboratory to study changes in signaling within tissues from patients who have received targeted therapies. A phase I working group headed by Razelle Kurzrock, M.D., Dr. Herbst, and Frank Giles, M.D., is developing hypothesis-driven trials of new agents, and Dan Karp, M.D., has established a 17-bed Clinical and Translational Research Unit to facilitate close observation and frequent sampling of blood and tissue.

Regardless of whether the patient is on the giving or receiving end, participation in translational research benefits everyone. ●

For more information, *contact Dr. Bast at (713) 792-7743.*

New Tests Cou to Chemotherap in Patients with

by Katie Prout Matias

Intensive research over the past several years has made breast cancer one of the most well-understood cancers and led to the development of several new drugs that can prolong survival. Because of these life-prolonging treatment options, the mortality rate from breast cancer has dropped about 2% each year since the late 1980s in both the United States and Western Europe. However, oncologists still have no good way of determining which treatment is best for an individual patient or whether a patient will respond to a particular treatment. This is especially true for chemotherapy.

Several chemotherapy regimens are available for patients with newly diagnosed breast cancer, but no regimen is effective in more than 50% to 60% of patients. Therefore, each patient has only about a 50% chance of benefiting from any given treatment, and many patients receive costly and toxic treatments that do not work.

To solve the problem of determining which chemotherapy regimen will work best in a particular patient, a team of researchers led by Lajos Pusztai, M.D., Ph.D., an assistant professor in the Department of Breast Medical Oncology at The University of Texas M. D. Anderson Cancer Center, has set out to develop a tumor gene–screening test to predict the efficacy of chemotherapy regimens. Fifteen percent to 30% of patients with newly diagnosed breast cancer have a complete pathologic response to chemotherapy; that is, all microscopic evidence of invasive tumor

ld One Day Predict Response py and Presence of Metastatic Disease n Breast Cancer

To determine which chemotherapy regimen will work best in a particular patient, **Dr. Lajos Pusztai**, *an assistant professor in the Department of Breast Medical Oncology, is developing tumor gene–screening tests to predict the efficacy of chemotherapy regimens for patients with newly diagnosed breast cancer. Here he holds a gene chip that can measure the presence or absence of 20,000 genes per patient tissue sample; the information is converted to numbers that represent the gene expression profile.*

cells disappears. "These patients still require surgery, but their long-term outcome is very good, and most of these individuals will be cured, regardless of how aggressive their disease appeared before starting chemotherapy," said Dr. Pusztai.

The researchers in Dr. Pusztai's team took tumor tissue samples from more than 80 patients newly diagnosed with breast cancer and examined more than 20,000 genes in each specimen. The patients were then given paclitaxel, 5-fluorouracil, doxorubicin, and cyclophosphamide (T/FAC, a commonly prescribed regimen at M. D. Anderson). Six months later, the patients underwent cancer surgery and pathologic analysis for response to the chemotherapy, and the gene expression profiles of patients who had a complete response were compared with those of patients who did not.

Analyzing the results from the first 24 patients, the researchers found a profile of 74 genes that was associated with complete response to chemotherapy. They incorporated these 74 genes into a mathematical algorithm to create a test that was 75% accurate and 50% sensitive in predicting who among a second sample of 21 patients would have a complete response to the same chemotherapy regimen. Patients whose tumors tested positive had a 75% chance of having a complete response to T/FAC. These results were presented at the plenary session of the 2003 annual meeting of the American Society of Clinical Oncology.

The researchers are now developing a second-generation T/FAC response predictor test based on a larger patient sample, which they hope will be more sensitive. They are also working on a portfolio of similar gene profile–based predictors for other commonly used preoperative chemotherapy regimens.

"If these new predictive tests prove similarly accurate and treatment regimen specific, it will fundamentally change how we select treatment," said Dr. Pusztai. "For example, if the predictor test indicated that several options would work equally well in a patient, her physician could choose the cheapest, shortest, and least toxic of those regimens. For patients in whom a complete response is unlikely with any of the current standard treatments, participation in a clinical trial with new drug combinations may be the most beneficial. This would also help speed up drug development because you could focus on developing new drugs for people who do not benefit from existing treatments."

While Dr. Pusztai's team is trying to improve survival rates by predicting who will respond favorably to chemotherapy regimens, other researchers at M. D. Anderson are trying to predict unfavorable outcomes.

Twenty percent to 30% of all women with apparently localized breast cancer will eventually die of metastatic disease. To identify these patients, researchers are using new blood tests to analyze what may be early metastatic events: cancer cells in the peripheral blood and bone marrow.

According to Kelly Hunt, M.D., an associate professor in the Department of Surgical Oncology at M. D. Anderson, circulating cancer cells are found in a large number of patients with breast cancer, even those with early-stage disease. "What that tells me is that these cancers are systemic from the very beginning," said Dr. Hunt.

Researchers want to determine how the circulating cells differ from primary tumor cells, whether they can grow outside the primary tumor site, and their effect on prognosis and treatment. A 2000 German study found that bone

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New Tests Could One Day Predict Response

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Dr. Massimo Cristofanilli, *an associate professor in the Department of Breast Medical Oncology, and* **Graciela Rodriguez**, *a graduate research assistant in the Department of Hematopathology, analyze a patient's blood sample. Dr. Cristofanilli is investigating whether the presence of cancer cells in peripheral blood is a marker for poor prognosis in patients with breast cancer.*

marrow disease was a good indicator of prognosis: Breast cancer was more likely to recur in patients with cancer cells in their bone marrow.

To build on this study, researchers at M. D. Anderson are participating in a multicenter American College of Surgeons Oncology Group trial in which bone marrow aspirations are being performed on patients with breast cancer to test for circulating cancer cells. The prognostic value of the presence of cancer cells in the bone marrow is then compared with that of sentinel lymph node biopsy to determine whether bone marrow aspiration could also be used as a prognostic tool.

"We've done well with breast cancer treatment over the past few decades, but there are still patients who fall through the cracks and for whom the treatment fails, so I think that we still need to refine the way that we identify which patients need which treatment," said Dr. Hunt. "I see bone marrow aspiration as one other way of getting a closer look at that patient and what's going on with her disease."

Bone marrow aspiration could also be used to determine the efficacy of common chemotherapy regimens. Massimo Cristofanilli, M.D., an associate professor in the Department of Breast Medical Oncology at M. D. Anderson, is giving preoperative chemotherapy to patients with bone marrow disease and testing their bone marrow to see whether the chemotherapy reduced the number of cancer cells.

Dr. Cristofanilli is also investigating the significance of cancer cells in the peripheral blood. In a study presented at the 2003 annual meeting of the American Association for Cancer Research, he and a team of researchers found that 24 of 41 patients with untreated metastatic breast cancer had cancer cells circulating in their peripheral blood. The researchers then correlated the number of circulating cells, or "tumor load," with treatment response and survival.

"It was very clear that the presence of cells and even the number of cells could predict the outcome of the patient. The patients who did not have cells had a very good prognosis. If they had cells, they had very short survival," said Dr. Cristofanilli. He pointed out that even patients with slow-growing estrogen receptor–positive tumors, which are not considered to be very aggressive, had poor survival rates if they had circulating tumor cells. "This is a very important point, I think, because this may help clinicians decide when to treat, when to treat aggressively, and when not to treat."

The most important question to ask, said Dr. Cristofanilli, is how the circulating cells differ from the original or primary tumor cells. The researchers want to determine whether the circulating cells have a different gene expression or microenvironment. Dr. Cristofanilli also wants to determine if a correlation exists between circulating tumor cells and patient response to various treatment protocols.

"I think the big picture is that clinicians want to be more aggressive in trying to improve our understanding of what a treatment does in patients," said Dr. Cristofanilli. "There have been significant advances in our knowledge of tumor biology, but the treatments themselves have essentially remained the same. We use the same type of treatment for every patient, whether their disease is newly diagnosed or metastatic, and we develop clinical trials using the same unselected approach. I think it's time to change. We need to be able to better select or stratify patients based on the biological makeup of their tumor and develop targeted treatment for every specific biological group or clinical scenario. Most of the currently proposed treatment modalities in breast cancer are modifications of standard chemotherapy regimens. In my opinion, just changing the schedule or the dose of administration will not have a significant impact on outcome for women with breast cancer. If we do not understand this fundamental concept and take the appropriate steps right now, in the next five years we'll be in the same situation." ●

FOR MORE INFORMATION, *contact Dr. Pusztai or Dr. Cristofanilli at (713) 792-2817 or Dr. Hunt at (713) 792-7216.*

HOUSE•CALL

Mind-Body Approaches for Patients with Cancer

Popular theories abound about what role the mind plays in cancer. At one end of the spectrum are those who claim that cancer develops as a response to stress and that it can even be cured by the mind. At the other end are those who believe that a patient's state of mind has no effect at all on the outcome of cancer treatment.

Although extremely stressful events such as the death of a spouse can alter the function of the body's immune system, there is no scientific evidence that these stress-induced changes in the immune system cause cancer, according to the National Cancer Institute. There is, however, evidence that the mind has a part to play in the health of the body.

It is not clear exactly how a person's mental state affects the cancer process, but the way a patient copes mentally and emotionally with the disease is vitally important. The body processes controlled by the nervous system can "plausibly affect resistance to cancer," according to an article quoted on M. D. Anderson Cancer Center's Complementary/Integrative Medicine Education Resources (CIMER) Web site (www.mdanderson.org/cimer). These processes include a person's behavior (for example, adherence to cancer treatment) as well as the hormonal, immune, and autonomic nervous systems. Therefore, comprehensive medical care "must take into account not only the biological dimensions of an illness but also the psychological and social factors that affect the whole person," according to Dr. David Spiegel in a *New England Journal of Medicine* editorial. Dr. Spiegel also wrote, "Curing cancer may not be a question of mind over matter, but mind does matter."

In fact, several complementary therapies are mind-body approaches that help patients manage symptoms, improve the effectiveness of their treatment, and increase their overall health and sense of well-being. These therapies are not cures. Instead they complement, or add to, the patient's medical treatment.

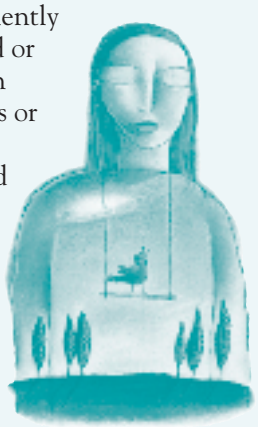
Some common mind-body practices include the following:

Support groups

In these groups, patients with cancer can discuss their feelings and concerns with other patients. A support group can meet in person, online, or via telephone. Some research indicates that participation in cancer support groups can reduce pain and ease distress.

Meditation

Meditation comes in many forms, but most involve concentrating on one's breathing or on a visual experience or silently repeating a word or phrase or certain physical postures or movements to release stress and free the mind from worries. For optimal results, meditation should be practiced once or twice a day for 10 to 20 minutes. The benefits to patients with cancer can include diminished pain, reduced stress hormone levels, improved immune function, and improved mood.



Hypnosis

Hypnosis is a state of focused attention. It is similar to sleep, except that the patient is alert and in control but deeply relaxed and open to suggestion. Hypnosis is usually performed by a hypnotist, but people can learn to hypnotize themselves. The American Cancer Society endorses hypnotherapy for reducing pain and stress and promoting relaxation.

Yoga

An ancient Hindu practice that includes breathing exercises, body postures, and sometimes meditation, yoga helps patients to relax and gain control of their bodies and minds. It also has been shown to relieve pain and anxiety associated with cancer and to improve immune system function.

While these and other mind-body techniques are helpful for most people, some may be harmful to specific patients. Before beginning any complementary therapy, patients should be sure to check with their cancer care team. ●

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

(800) 392-1611, Option 3, *within the United States, or*

(713) 792-3245 *in Houston and outside the United States.*

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Staff Publications

Below is a partial list of staff publications appearing in March.

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