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OncoLog

Harnessing the Immune System:
The Promise and Potential of Cancer Vaccines

by Rachel Williams

IMAGINE A VACCINE THAT STIMULATES THE immune system to seek out and destroy tumor cells. The notion seems futuristic—that is, until you're sitting across from Dr. Jeff Molldrem, listening to him describe how three simple subcutaneous injections of a 9-amino acid peptide antigen induced not only clinical but complete molecular remissions in several leukemia patients.

"We were startled," said Dr. Molldrem, M.D., (below) associate professor in the Department of Blood and Marrow Transplantation at The University of Texas M. D. Anderson Cancer Center. "Initially, we were just trying to see if we could boost immunity to the antigen we had identified—we didn't expect molecular remissions, especially in a phase I trial and in such a refractory group. That's never been described before

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Cancer Vaccines

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>
> **– Dr. Yong-Jun Liu**

for *any* vaccine," he said.

This promising—if preliminary—finding is the first clinical demonstration that complete molecular remission is possible with a peptide vaccine. The 45 subjects were patients with myeloid leukemias who had repeatedly failed every standard therapy and had life expectancies of less than a year. In response to the vaccine, 11 of the patients had objective clinical responses—and a few went into remission. Four years later, four of those patients are still in complete molecular remission—no evidence of leukemia in amplified DNA, down to one in a million cells. Furthermore, disease progression slowed in patients who showed an immune response but did not go into remission.

"Of course, these are early findings," cautioned Dr. Molldrem, who is the study's lead investigator. "We have much more research to do, especially in testing greater numbers of patients in each disease group." Toward that end, Dr. Molldrem and colleagues expect to open three more trials of the vaccine this year.

The peptide vaccine is but one example of promising work taking place in the burgeoning field of cancer immunotherapy. Developing the field is one of M. D. Anderson's highest research priorities, as evidenced by the creation of the Center for Cancer Immunology Research. Yong-Jun Liu, M.D., Ph.D., director of the center, speaks of the promise immunotherapy holds for cancer treatment.

"I think it is very possible that some type of cancer vaccine will be commercially available within the next decade," said Dr. Liu. (He refers, of course, not to a ubiquitous cancer prevention immunization, but to a vaccine that would be used in the treatment of a specific type of cancer.)

While scientists have long sought to find a way to use the power of the body's own immune system against tumors, recent scientific advances make the enterprise a little more feasible.

"A fundamental understanding of the immune system has only been developed over the last four decades or so, and that knowledge is critical for developing cancer vaccines," explained Dr. Molldrem. "For instance, one of the trickiest parts is to identify which antigens to direct the immune response against in any given tumor type. There can be up to 100,000 different proteins and protein variants getting turned over at different times in a cell, so trying to identify which ones the T-cell actually 'sees' is kind of like finding a needle in a haystack But now we have a molecular scale for understanding how it works, which is an important tool for directing immune reactions against a tumor."

Dr. Liu stresses that, while there are many promising studies under way, the field of cancer immunology is still in its infancy. "We are still trying to refine what we know about the basic principles of the immune system and how it detects invaders. It's the only way to develop truly effective cancer vaccines."

While, overall, the immune system is very effective in protecting against viral, bacterial, and other infections, it is not very well developed for getting rid of cancer. One reason may be that cancer does not really threaten the existence of the human species, since most cancers occur after age 65. In any case, because cancer doesn't present itself as an outside invader, the immune system's cellular detection systems apparently don't distinguish well between the normal tissue and tumor tissue and as a result cannot efficiently get rid of tumor cells.

Dr. Liu said that the existence of autoimmune diseases indicates that the immune system is capable of attacking self-tissues; the trick is learning how to get it to attack malignant tissue instead. By fully understanding how the immune system detects bacteria and viruses, we can develop ways to manipulate it to destroy cancerous cells as well.

Eventually, immunotherapy could offer distinct advantages for cancer treatment. "Hypothetically, once the immune system has been sufficiently stimulated, it would be able to find and destroy every single tumor cell throughout the body," said Dr. Liu.

Immunotherapy has potential not only for treatment of disease but also for prevention of recurrences as well, because of the immune system's ability to "remember" the antigen. Finally, it could be used as a preventative measure for healthy people who are at high risk of developing certain cancers.

Dr. Molldrem's peptide vaccine, for example, has several potential clinical applications. "About two thirds of people with acute myelogenous leukemia go into a first remission with treatment, but most relapse and few

survive," said Dr. Molldrem. "We're planning a study to look at whether administering the vaccine during that first remission can make the remission longer, or possibly even permanent."

The vaccine also has potential use for prevention. "People who undergo chemotherapy are at increased risk of developing the leukemia-related blood disorder myelodysplastic syndrome," he explained. "Eventually, the hope is that maybe that risk could be reduced or eliminated with a vaccination."

Stimulating T-cells

M. D. Anderson currently has a number of immunotherapy studies underway, but efforts are primarily focused in three areas. "Right now, our vaccine development studies are concentrated in leukemia, lymphoma/myeloma, and melanoma," said Dr. Liu. "That's because we have very strong translational research programs in these areas at M. D. Anderson, as well as very active immunotherapy programs." Findings from these areas are likely to have applicability in other areas as well.

Dr. Molldrem developed the peptide vaccine for leukemia about 10 years ago, here at M. D. Anderson, whereas both Larry W. Kwak, M.D., Ph.D., and Patrick Hwu, M.D., recently were recruited from the National Cancer Institute to lead immunology development in the departments of Lymphoma/Myeloma and Melanoma, respectively. The two brought active programs and a wealth of research with them.

Research into vaccines for melanoma has produced limited but dramatic results, according to Dr. Hwu, who is chair of the Department of Melanoma. "We use interleukin 2 (IL-2) to stimulate T-cells, and it's brought about long-term remissions in some of the patients, despite severe metastatic disease. Of course, these dramatic responses happen in the minority of patients, but it shows that if we can stimulate the T-cells, we might have long-lasting effects against cancer."

Dr. Hwu explained that immunotherapy for melanoma can be done in one or more of the following ways:

- Stimulating the immune system with cytokines
- Using cancer vaccines to try to stimulate the immune cells
- Isolating dendritic cells, pulsing them with antigens, and then giving them back to the patient, or
- Isolating T-cells, growing them to large numbers, and then giving them back to the patient (called adoptive T-cell transfer or adoptive immunotherapy).

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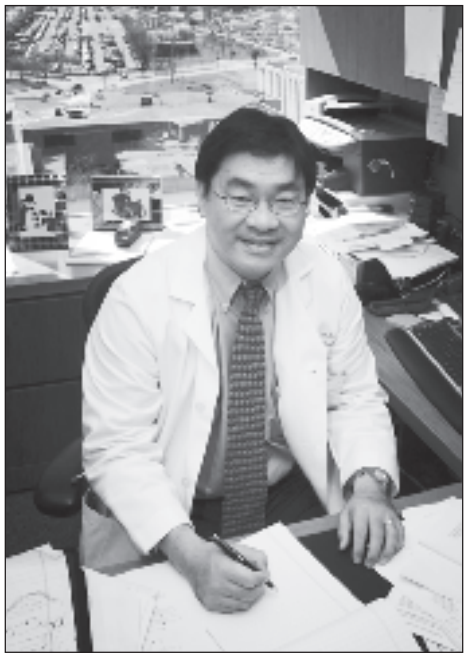
>
> **– Dr. Patrick Hwu**



Dr. Hwu's previous studies demonstrated that the T-cell transfer method brought about objective clinical responses in 50% of patients with metastatic disease—which is a higher response rate than any other therapy for metastatic melanoma. More promising still are recent mouse models that suggest that combining these T-cells with dendritic cells may bring about an even greater clinical response.

"The fact that the treatment is individualized is what makes it challenging," he said. "We have to come up with the best way to grow the cells sufficiently and easily in every patient. We are trying to develop a way to make this process easier and more widespread, just like bone marrow transplants."

Amassing knowledge

Early vaccine research in lymphoma actually dates to initial studies begun in mice 30 years ago upon discovery of a very well-defined lymphoma tumor antigen, said Dr. Kwak, chair of the Department of Lymphoma. "The antigen truly distinguishes the tumor B cells from normal counterparts, making any immune response exquisitely specific to those cells."

Dr. Kwak tested a "second generation" lymphoma vaccine about 15 years ago in a successful and highly publicized human study. Since then, he has conducted a series of phase II trials of the vaccine, in which up to 75% of study participants with low-grade lymphoma achieved molecular remissions and long-term, disease-free survival. Currently, Dr. Kwak is involved in a national, multicenter phase III trial of the vaccine he pioneered.

He's also investigating the use of a similar vaccine in another intriguing new area of immunotherapy research. "In collaboration with the Blood and Marrow Transplantation Department, we're doing phase I testing of a similar vaccine in multiple myeloma in the setting of bone marrow transplantation," he said. "Instead of vaccinating the patient, we actually vaccinate the bone marrow donor. It's the principle of breaking immunological tolerance.

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Cancer Vaccines

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> **"It's the principle of breaking immunological tolerance."**
>
> **– Dr. Larry Kwak**

Then we transfer the T-cells from the donor to the recipient. We're really excited about that. That's a new initiative that's just coming out of the laboratory and is happening here."

Dr. Kwak came to M. D. Anderson because of just this kind of opportunity—to advance immunology research in collaboration with researchers, scientists, and doctors across disciplines. As Dr. Liu explains it, the Center for Cancer Immunology Research is an important hub for collaborations that lead to the translation of findings from basic immunology research into clinical trials and ultimately new and better treatments. "Here, basic immunologists and clinical immunologists are together in one building, and the proximity provides an easy, natural opportunity for collaboration," said Dr. Liu. "We have the critical mass here—that's really exciting." ●

For more information, *contact Dr. Molldrem at (713) 563-3318, Dr. Liu at (713) 563-3203, Dr. Hwu at (713) 792-2921, and Dr. Kwak at (713) 745-4244.*

Considering Prophylactic Surgery

Now that genetic testing can identify women with BRCA1 or BRCA2 mutations that put them at high risk of developing breast or ovarian cancer, new questions have emerged for doctors and their patients—in particular, the complex issue of prophylactic surgery.

by Ellen McDonald

The prospect of undergoing prophylactic mastectomy and oophorectomy never enters the minds of most women (or their physicians) over a lifetime. For women like [redacted], however, that prospect can take on a stark immediacy once cancer is diagnosed in a close relative.

"I knew that a lot of people in my family had died of breast and ovarian cancer," explained [redacted]. "Then, when my sister got breast cancer and learned she had a genetic defect, that was kind of a wake-up call." After having genetic testing at M. D. Anderson Cancer Center and discovering that she had a *BRCA2* mutation, [redacted] decided last year to undergo a bilateral mastectomy and, later, an oophorectomy with a hysterectomy for cancer prophylaxis.

"Oddly enough," the 45-year-old lawyer remarked, "I was just very comfortable with my decision." That was even before pathologic examination showed ductal carcinoma *in situ* in the left breast and some abnormal cells in the right breast.

Although removing seemingly healthy breasts and ovaries to prevent a future cancer seems a drastic step, this option may currently offer the best hope for prevention in some women with identified mutations.

"When genetic testing first became available in the mid-1990s, nobody really knew how effective preventative

> **"...within the past six years or so, the effectiveness of these prophylactic surgeries has been confirmed."**
>
> **– Dr. Louise Strong**

Physicians and genetic counselors at M. D. Anderson help patients make informed decisions. Here, genetic counselor **Julie Erlichman**, *M.S., and* **Dr. Banu Arun**, *an associate professor in the Department of Breast Medical Oncology, review patient education materials.*

surgeries might be; it was not such a sure thing that you could actually remove enough of the questionable cells to have a big effect. The concern was that people would go through these major surgeries and then a few years later develop cancer anyway," said Louise Strong, M.D., a professor and chair of the Department of Clinical Cancer Genetics at M. D. Anderson. "But within the past six years or so, the effectiveness of these prophylactic surgeries has been confirmed." For example, studies in women with deleterious mutations of *BRCA1* and *BRCA2* have shown a significant decrease in the risk for breast cancer in those who undergo bilateral prophylactic mastectomy (90–98%) and of ovarian cancer in those who undergo prophylactic oophorectomy (over 90%).

Physicians and genetic counselors at M. D. Anderson help women make informed decisions by providing risk assessment, discussing risk-reduction options, and devising an appropriate management strategy. Ideally, genetic counselors see patients very early in this process: "We really like patients to have extensive counseling even before they have genetic testing because we can talk to them about the potential emotional consequences and family dynamic issues that might come up with different testing results," noted Julie Erlichman, M.S., a genetic counselor in the Department of Clinical Cancer Genetics. "Once we give them the results, we talk to them generally about what their options are and then refer them to physicians for the more in-depth discussion of what is involved."

Banu Arun, M.D., an associate professor in the Department of Breast Medical Oncology, said that for patients with a deleterious *BRCA1* or *BRCA2* mutation, whose lifetime risk for breast cancer she estimated as anywhere between 50 and 80%, she presents all available risk-reduction options. These include frequent screening by mammography, magnetic resonance imaging, and clinical breast examination; chemoprevention with tamoxifen or other drugs currently under study; and prophylactic surgery, which can mean mastectomy, plus or minus oophorectomy; or oophorectomy with no mastectomy.

"I tell our patients that if they opt to have an oophorectomy because their ovarian cancer risk is high as well, their breast cancer risk will also be decreased anywhere between 30 and 50%," said Dr. Arun. Regarding prophylactic mastectomy, she noted, "In genetically high-risk women, mastectomy is one of the valid options, but it is a personal choice not only whether to have the surgery, but when to have it. They have time to think about their options, and the best option for each person may be different."

Like Dr. Arun, Funda Meric-Bernstam, M.D., a surgeon and an assistant professor in the Department of Surgical Oncology, tells patients that choosing prophylactic mastectomy is an enormous decision that should not be rushed. She encourages them to consider all their options and decide from the perspective of their own perceived risk; current, constantly evolving scientific information; and what they expect to happen in the field and to themselves within the next 10 years, based on conversations with genetic counselors, physicians, and possibly others who have faced the same decision.

For BRCA-positive women who want to reduce their risk for breast cancer as much as possible, Dr. Meric-Bernstam observed, "Studies suggest that with mastectomy we can decrease their risk by 90 to 95%, so bilateral prophylactic mastectomy is the gold standard for prevention. The important thing to consider is that no surgery is minor surgery, even if you're in good health. With reconstruction, we can get a cosmetically good result; however, it won't be a natural breast, it won't have normal sensation, and there may be substantial consequences from a psychosocial perspective.

"I tend to meet with patients at least twice to go over all of this," Dr. Meric-Bernstam continued, "giving them at least three months from our first meeting to absorb the information before we go over it again. I want them to be sure this is what they want to do before proceeding. If a woman decides on surgery, they meet with the plastic surgeons a few times to come up with the most conservative reconstruction that will give the most cosmetically pleasing result."

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Considering Prophylactic Surgery

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Whereas prophylactic mastectomy is presented as one of the risk-reduction options available to women with *BRCA1* and *BRCA2* mutations, prophylactic oophorectomy is presented more as a necessity for these women. Dr. Karen Lu, M.D., an associate professor in the Department of Gynecologic Oncology, provided the grounds for this difference: "Screening for ovarian cancer has never been proven to be effective. For a woman who is at very high risk, prophylactic oophorectomy has been shown definitively to decrease risk by greater than 90%.

"Consequently," Dr. Lu noted, "we recommend that after childbearing known mutation carriers undergo prophylactic oophorectomy. Oral contraceptives can be a good option for younger women not ready for surgery yet."

In terms of what the future holds, Dr. Meric-Bernstam noted that ongoing attempts at M. D. Anderson and other institutions to develop genome-specific chemopreventive agents and a blood test that can detect breast cancer earlier than is currently possible may obviate or at least decrease the need for prophylactic mastectomy. Similarly, Dr. Lu spoke hopefully of new markers being identified that will lead to better detection of ovarian cancer and possibly decrease the need for prophylactic oophorectomy.

[redacted] believes that both her son and daughter should ultimately be tested to see if they carry the *BRCA2* mutation. However, on the advice of her M. D. Anderson physicians, she told her 12-year-old daughter not to worry about testing until she was in her 20s at the earliest because the state of cancer prevention, detection, and treatment may have changed substantially by then. ●

For more information, *contact Dr. Louise Strong at (713) 792-2589, Julie Erlichman, M.S., at (713) 745-7391, Dr. Banu Arun at (713) 792-2817, Dr. Funda Meric-Bernstam at (713) 745-4453, or Dr. Karen Lu, at (713) 745-8902.*

IN BRIEF

Molecular Markers: Focusing on Individualized Cancer Care

Based on a $5 million gift by the Kleberg Foundation, the new Robert J. Kleberg, Jr. and Helen C. Kleberg Center for Molecular Markers (the Kleberg Center), currently under construction, will provide housing for research into new advances in molecular marker research. Researchers will find ways to identify individuals at high risk for developing specific types of cancer, develop screening approaches for early diagnosis of cancer, and tailor therapy to the genetic make-up of each patient.

"Our goal is to treat each patient's tumor based on what is happening with the biology of that person's cancer," said Gordon Mills, M.D., Ph.D., chair of the Department of Molecular Therapeutics and director of the Kleberg Center. "If we know which proteins are altered when cancer cells divide and multiply, we can better determine how to treat those proteins to stop cancer growth."

The Kleberg Center's research labs will bring together ongoing efforts to evaluate changes in tumor DNA, RNA, and proteins and determine the consequences of those changes. They will enhance the collaboration of researchers in evaluating the genetic make-up of patients to identify molecular markers for the possibility of developing cancer and for predicting susceptibility to toxic effects of particular drugs. In addition, the Kleberg Center program will support clinical trials to determine the value of molecular markers in predicting which patients are at high risk for developing cancer or have an early cancer.

The Kleberg Center will be a collaborative program, built on core programs already established at M. D. Anderson, such as that in genomics and proteomics, and will include several research programs within the institution, such as those in lung, breast, prostate, and leukemia.

"We'll establish pilot programs in certain disease sites and then share what we learn with other disease sites," said Mills. "For instance, what we learn about molecular markers in lung cancer may be translated to breast cancer. This program is not disease-site specific."

Genetic Blueprinting: Predicting Response to Treatment

For the first time, researchers have been able to predict how patients would respond to different treatments for esophageal cancer, based on individual genetic profiles.

Researchers at M. D. Anderson Cancer Center report that six different gene variants can predict an improved outcome in patients treated with two different chemotherapy drugs and/or with radiation therapy. For example, a combination of several gene variants in patients treated with one type of chemotherapy (5-FU) more than doubled survival to 51 months, compared with 25 months in patients treated with the same drug who did not have these variants.

They say the findings represent a leap forward in the goal to provide tailored therapy to individual patients that offers a genetic blueprint for gauging the potential effectiveness of all common esophageal cancer treatment, not just an analysis of how one or two "candidate" genes respond to a single treatment.

"Our data strongly suggest that combined pathway-based analysis may provide powerful clinical outcome predictors for esophageal cancer as well as for other cancers," stated the study's lead author Xifeng Wu, M.D., Ph.D., a professor in the Department of Epidemiology.

"This points to a promising new direction for cancer pharmacogenetics," she said. "Our hope is to have a gene chip one day that can analyze a patient's genetic makeup and help physicians predict response to a wide variety of therapeutic drugs before treatment even begins." ●

HOUSE•CALL

Chemotherapy and Hair Loss

Coping with a common side effect of cancer therapy

Chemotherapy often causes hair loss, a visible side effect of cancer treatment and a source of emotional distress for those coping with the disease.

Chemotherapy works by killing rapidly growing cancer cells, and in the process, many rapidly-growing healthy cells die, too, such as cells in the hair follicles. The hair loss that results can drastically affect a person's appearance and self-image. Here are answers to some common questions that might help you understand and cope with chemotherapy-induced hair loss.

Why does chemotherapy cause hair loss?

Because anticancer drugs don't discriminate between the cells they destroy, they often kill normal cells like those in hair follicles, resulting in rapid hair loss. This loss can occur on all parts of the body—scalp, face, arms, legs, underarms, and pubic areas, and can vary in degree from mild thinning to total hair loss.

Can hair loss be prevented during chemotherapy treatment?

There is no known way to prevent chemotherapy-induced hair loss. However, not all chemotherapy medications cause hair loss. You should consult with your doctor about the type of treatment recommended for you and what its side effects are likely to be. Whether or not you lose your hair depends in part on the specific medication and dosage administered.

When will I lose my hair, and is the hair loss permanent?

Depending on the type of chemotherapy, hair loss can start anywhere from seven to 21 days after treatment begins. When hair loss begins, you may notice a little dull pain or a tingling sensation of the scalp, and the loss can be sudden or gradual. But the good news is that hair loss caused by chemotherapy is temporary. If you lose hair, it will almost always grow back after you have completed treatment and some people even start to get their hair back while they are still having treatments. The time it takes to regrow hair can vary widely, from three to 12 months. Occasionally, the new hair has a different texture (e.g., curly instead of straight) and/or color (e.g., dark instead of light).

If you lose hair, *it will almost always grow back after you have completed treatment.*

How can I care for my scalp and hair during chemotherapy?

To protect your hair from added stress, use mild shampoos and soft hair brushes. Also, avoid using heat appliances, such as blow dryers, curling irons, and hot rollers. If you must use heat appliances, use the lowest setting. If you experience hair loss, keep your scalp clean and moisturized to prevent skin breaks. Use a sunscreen, sun block, hat, scarf, or wig to protect your scalp from the sun.

What are some tips for looking good despite hair loss?

One option is to consult a wig specialist before you start treatment for help with selecting a wig that closely matches the color, style, and texture of your own hair. Many insurance companies will cover all or part of the cost of a wig, but if that option is not available to you, you may be able to claim the purchase on your income tax as a medical deduction. Some people opt for cutting their hair very short or shaving completely at the beginning of treatment just to simplify the process. Shorter styles often appear thicker and fuller, and will make hair loss easier to manage if it occurs. Other options are to wear creatively accessorized turbans, scarves (with scarf pads worn underneath), hats, or bandanas. Still others decide to forgo headwear and embrace baldness.

Where can I get more information?

Some hospitals and community centers offer complimentary barber and beauty services through the public service program Look Good…Feel Better, including complimentary consultations to help patients explore headwear options. If yours doesn't, ask where you can get such products and services locally, or contact the American Cancer Society at (800) ACS-2345 or www.cancer.org. ●

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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K. Dupree

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DiaLog

Redefining Success in Cancer Care

Michael Fisch, M.D., M.P.H.
Medical Director, Community Clinical Oncology Program

Since my first days at M. D. Anderson Cancer Center, I have been inspired by the photographs on the walls of people who have been successfully treated here. These are people of various backgrounds and ages, but the attribute they all share is that they have defeated the cancer that threatened their lives. They appear triumphant, and below their names and ages is the name of their malignancy crossed out in red ink. These photographs cause me to reflect on this question: How do *I* define success in caring for patients with cancer?

The people in those photos are inspiring success stories, no doubt—after all, Making Cancer History® is M. D. Anderson's ultimate goal. Yet something seems to be missing; the pictures don't quite tell the whole story. It reminds me of a baseball player who says his mission is to win the World Series. While true, it doesn't fully explain the meaning of his efforts each inning of each game throughout the season. Why does he continue to put on his uniform, show up at the ballpark, and sprint for fly balls when the goal of winning the World Series is no longer attainable?

Palliative care physicians often counsel patients about the possibility of finding hope and meaning, even in the face of disappointment or very difficult circumstances. A well-known work in this realm is that of Dr. Viktor Frankl, a psychiatrist and survivor of the Holocaust who wrote *Man's Search for Meaning*. One of the statements in his book that I found most striking is this imperative: *Live as if you were living for the second time, and had acted as wrongly the first time as you are about to act now.* At first it seems confusing, almost like something you might find in a fortune cookie. But with further reflection, I think this statement points toward a more satisfactory definition of success in cancer care.

Success is the act of striving to achieve the very best for our patients, whether it's the first inning or the ninth. It's thinking and acting with care and skill so that we achieve the most thorough understanding of a person's illness, the best possible relationship with the patient and the family, the most ideal delivery of care through teamwork with other health professionals. We help patients maximize both their length of life and quality of life while preserving their dignity each step of the journey.

In the course of striving to give patients our best, sometimes we eradicate their cancer. Sometimes we can't. Regardless, each patient we treat could be a model of success in our campaign—as long as we are mindful of what it is we are really doing in the practice of cancer medicine. This may sound strange, but it's true—success is all about us. ●

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