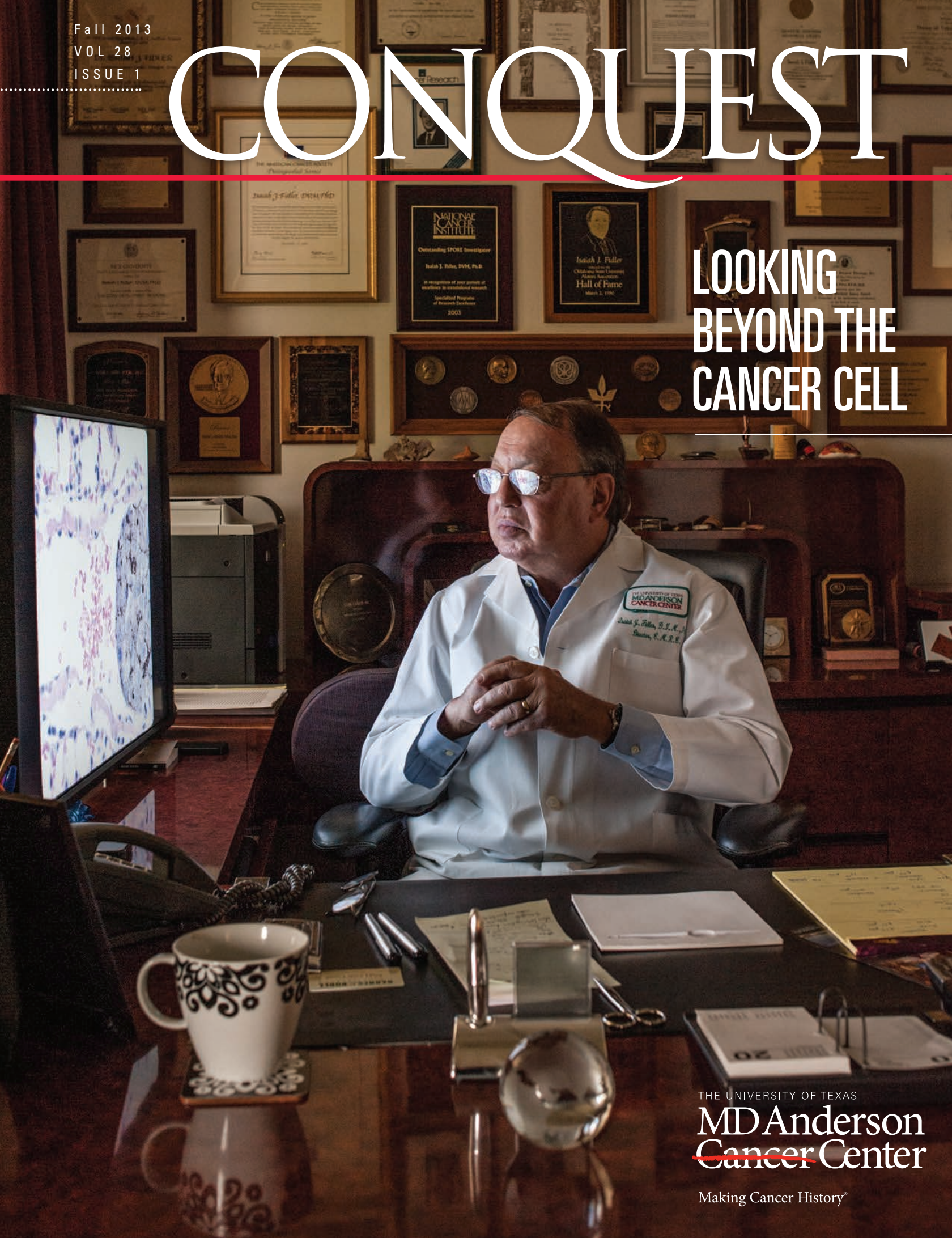


Fall 2013  
VOL 28  
ISSUE 1

# CONQUEST

LOOKING  
BEYOND THE  
CANCER CELL



THE UNIVERSITY OF TEXAS  
**MD Anderson  
Cancer Center**

Making Cancer History®



## MISSION

The mission of The University of Texas MD Anderson Cancer Center is to eliminate cancer in Texas, the nation, and the world through outstanding programs that integrate patient care, research and prevention, and through education for undergraduate and graduate students, trainees, professionals, employees and the public.

## VISION

We shall be the premier cancer center in the world, based on the excellence of our people, our research-driven patient care and our science.

We are Making Cancer History®.

## CORE VALUES

### Caring

By our words and actions, we create a caring environment for everyone.

### Integrity

We work together to merit the trust of our colleagues and those we serve.

### Discovery

We embrace creativity and seek new knowledge.



**On the cover: Isaiah Fidler, D.V.M., Ph.D., has dedicated his career to unraveling the complexities of metastasis. In 2013, he received the prestigious Medal of Honor in Basic Science Research from the American Cancer Society.**



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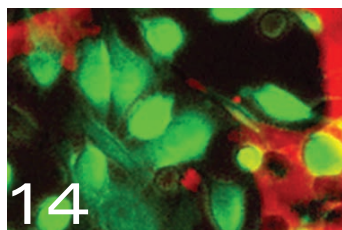
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In 1889, Stephen Paget, an English surgeon and pathologist, hypothesized that metastasis (the spread of cancer) did not occur randomly. It took nearly a century before Isaiah Fidler came along to prove him right.

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Obesity-related conditions, such as heart disease, stroke, type 2 diabetes and certain types of cancer, cause deaths that might have been prevented. At MD Anderson, behavioral scientists, epidemiologists and clinical cancer prevention experts are addressing the issue on several fronts.

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Some might call it fate that three scientists came together at MD Anderson to speed research and drug development in the relatively new area of epigenetic marks, damage to which — unlike DNA mutations — can be reversed.

# COMMENTARY

## How MD Anderson is preparing for health reform

By Thomas W. Feeley, M.D.

Since the passage of the Affordable Care Act (ACA) in 2010, we've heard a tremendous amount about health care reform in America. Many of the bill's provisions take effect in 2014, so it's reasonable to ask what MD Anderson is doing to prepare.

Since a landmark piece of legislation like the ACA has many components, there's a lot of uncertainty about what effect different provisions will have on our patients and organization. Rather than thinking about how we're preparing for specific aspects of the bill's implementation, it's probably best to think of how MD Anderson is preparing for a changing health care delivery environment.

MD Anderson's Institute for Cancer Care Innovation focuses on demonstrating and continually improving the value of MD Anderson care for our patients. In health care, value is defined as the balance between the outcomes we achieve and the costs required to achieve them. Using that framework, let's look at what we're doing.

### CANCER CARE COSTS

We constantly hear that the costs of health care in America are the highest in the world, yet for many people, our health outcomes are not the best. At MD Anderson, we know that multidisciplinary, research-driven patient care offers patients the best possible outcomes, but our cost structure is extremely high. We also know that in the future it's unlikely we'll be paid more for our care.

### SO WHAT ARE WE DOING TO CONTROL OUR COSTS?

Throughout the organization, teams have been looking for opportunities to control costs, reduce redundancies, decrease practice variability and achieve administrative savings without adversely affecting the quality of the care we provide. We'll grow more slowly and do more with less. We must:

- Optimize the performance of clinical professionals to practice to the full extent of their education, training and licensure.
- Limit the services we provide, especially those that do not have a significant effect on patient outcome.

These are huge challenges for an organization that's had an abundance of resources and achieved tremendous growth over the past 15 years.

### CANCER CARE REIMBURSEMENT

Currently, cancer care is paid for through America's long-standing fee-for-service system. Every procedure and visit is billed separately through a complex and costly process. Now, we're investigating new reimbursement systems that pay for episodes of care for specific diseases, which, in turn, provide payments to us for the defined period of time we care for a patient.

Developing such a system requires that we actually know our true costs of care delivery. We've partnered with Harvard Business School to develop a new cost accounting system for health care — one that actually measures exactly how much each step in the care delivery process costs. This system, called time-driven, activity-based costing, has created the framework to begin to develop models for episode-based payments as our reimbursement system gradually changes. It also provides an opportunity to identify our highest-cost processes and address them directly through performance improvement.

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**Our ultimate aim is to demonstrate the best patient-centered outcomes of care achieved at the lowest possible cost.**

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**Thomas W. Feeley, M.D., is the Helen Shafer Fly distinguished professor and head of Anesthesiology and Critical Care, as well as head of MD Anderson's Institute for Cancer Care Innovation.**

## CANCER QUALITY METRICS

To constantly improve, we must measure the outcomes of our care. The Affordable Care Act mandated that we measure and report cancer metrics by 2014.

We'll do that, and we've taken this a step further. We're developing programs to better understand which outcomes of care are really important to our patients, and how we can develop measurement systems to report them internally for improvement and externally for others to see.

We're conducting patient focus groups to ask them which outcomes are important, and how they want to receive this information. Our ultimate aim is to demonstrate the best patient-centered care at the lowest possible cost.

In addition to the Institute for Cancer Care Innovation, there are many MD Anderson teams involved in our preparations.

- Governmental Relations monitors legislative activities in Washington and Austin and provides expert opinion as needed.

- Health Policy is engaged in our state activities, including changes to the Medicaid program and cancer control.
- Teams in clinical operations, especially Performance Improvement, have been identifying opportunities to improve patient flow through our system.
- Clinical Cancer Prevention has been preparing to handle the increased number of patients who will have cancer prevention and screening available to them through prevention provisions of the ACA.

The bottom line is that while the ultimate fate of the act is uncertain, the need for health reform is real, and we'll be affected over the coming five to 10 years. We must find ways of making more effective use of our existing resources to continue Making Cancer History®.



# FRONTLINE

## A DRUG. A DISEASE. THREE STUDIES. FOUR INVESTIGATORS.

### Analyzing bevacizumab for glioblastomas

By Laura Sussman, William Fitzgerald and Sandi Stromberg

**G**lioblastoma remains the most common and lethal of brain cancers. So it isn't surprising that when a drug shows early promise, MD Anderson clinical researchers design protocols to understand how effective it will be for patients — especially in a disease that has too few effective treatments.

At the 2013 annual meeting of the American Society of Clinical Oncology (ASCO), four investigators presented their findings in studies with bevacizumab (Avastin) for patients newly diagnosed with glioblastoma.

The drug, which blocks blood vessel growth that feeds the tumor, first showed promise in patients when clinicians reported positive results treating the disease under approved compassionate use. Numerous studies then found similar results: 35% to 40% tumor shrinkage in more than 50% of the patients — with a 50% progression-free survival rate in 30% of them. With these findings in May 2009, the U.S. Food and Drug Administration granted accelerated registration of bevacizumab for recurrent, re-growing glioblastoma.

#### STUDY NO. 1: Bevacizumab fails newly diagnosed glioblastoma patients

Before a trial led by Mark Gilbert, M.D., professor in Neuro-Oncology, no Phase III, randomized, double-blind study had been conducted with this drug in glioblastoma. Findings from this trial were significant and highlighted at the plenary session of ASCO.

"When we launched the study, those in the field of brain cancer — both the scientific and patient communities — were excited," he says. "Bevacizumab had recently received approval for recurrent disease, and we knew some physicians were already giving it as frontline therapy, even with virtually no data to support that decision. It was important from a patient care and regulatory standpoint that we conduct this trial."

Results showed that bevacizumab failed to increase overall survival (OS) — or statistically significant progression-free survival (PFS) — in newly diagnosed patients. However, Gilbert stresses that the study still found the drug had some use in managing the disease.

"Ultimately, our study showed that bevacizumab has the same benefit whether given early or late, and, because of the risk of extra toxicity upfront, its use can be reserved as a later treatment for most patients," he says.



Mark Gilbert, M.D.

#### STUDY NO. 2: Diagnostic tool may help predict right patients for bevacizumab

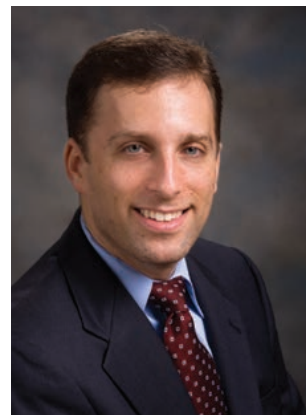
A new test may help identify newly diagnosed glioblastoma patients more likely to benefit from bevacizumab, according to a Radiation Therapy Oncology Group, large, multicenter, Phase III trial.

"We wanted to identify those most likely to benefit from bevacizumab and use that information to develop a diagnostic tool that can predict the best patients for the drug," says Erik Sulman, M.D., Ph.D., assistant professor in Radiation Oncology and lead author on the study.

As part of the trial, patients were required to submit specimens for molecular analysis. The umbrella study data also included molecular stratification that measured the degree of mesenchymal gene expression. These genes are known to function in cancer cell invasion and in establishing a new blood supply for the tumor, a function bevacizumab is designed to prevent.

Based on this association, researchers modeled a novel gene that, when expressed, predicts outcomes specific to those treated with bevacizumab. Plans are to determine whether this can be used for newly diagnosed glioblastoma.

"We'll use data from the remaining patients on the trial to confirm these findings," Sulman says. "We hope the test will be validated and used as a diagnostic tool to select patients for initial treatment with bevacizumab. Then, we plan to look beyond glioblastoma to see if it could benefit other tumor types currently treated or in clinical trials with the drug."



Erik Sulman, M.D., Ph.D.

**STUDY NO. 3:****Bevacizumab reduces cognitive function and quality of life**

In the past decade researchers and pharmaceutical companies have become more aware of the need to understand treatment side effects, as well as a drug's effectiveness. Reducing patients' symptom burdens means that they may survive with reasonable quality of life.

To understand the symptom burden of bevacizumab, two MD Anderson investigators joined a large, national, multicenter Phase III trial, under the auspices of the Radiation Therapy Oncology Group: Jeffrey Wefel, Ph.D., associate professor in Neuro-Oncology, a senior author on the study, and Terri Armstrong, Ph.D., adjunct professor in the same department and professor at The University of Texas Health Science Center at Houston School of Nursing.

The objective was to understand the clinical benefit of adding bevacizumab to standard chemotherapy and radiation with maintenance temozolomide, versus those who received a placebo and standard treatment. Instead of the traditional OS and PFS endpoints, however, they wanted to understand the potential impact on patients' quality of life.

Using objective tests of cognitive function and subjective measures of symptoms, 507 patients were evaluated at diagnosis and at intervals throughout treatment, as long as scans showed their tumors were not progressing.

**Putting the total picture together**

At the beginning of the study, patients' neurocognitive function in both groups was below healthy population norms. Analyses showed those treated with bevacizumab, compared to those treated with the placebo, demonstrated greater decline in global neurocognitive function, executive function (skills like planning, organizing and multi-tasking) and thought processing speed. In addition, patients' subjective report of symptoms and the interference of these symptoms with their daily life were greater in those treated with bevacizumab.

Additionally, baseline performance and early change (through week 10) in symptoms, quality of life and neurocognitive function were prognostic for both PFS and OS.

"We found that patients with worse cognitive function at baseline, and those who experienced cognitive decline after concurrent chemotherapy and radiation — with or without bevacizumab — were at greater risk for shorter PFS or OS time," Wefel says.

"The idea of our research was to put together the total picture of this treatment, not only how it affects the tumor, but how it affects patients and how they go about their lives," Armstrong says. "It was our hope that this treatment would improve life for them, but that just wasn't the case. For many, both tumor and treatment-related symptoms were worse and continued to get worse over time."

**Jeffrey Wefel, Ph.D.****Terri Armstrong, Ph.D.****See MD Anderson news online**

For more information on these and other basic, translational and clinical research findings, see MD Anderson's Newsroom ([www.mdanderson.org/newsroom](http://www.mdanderson.org/newsroom)) and Cancer Frontline ([www2.mdanderson.org/cancerfrontline](http://www2.mdanderson.org/cancerfrontline)).

# Creating an umbrella of care

## General Internal Medicine

By Sandi Stromberg

While MD Anderson is a cancer center with hundreds of oncology experts, the body can have other health issues: hypertension, diabetes, heart disease, osteoporosis, to name a few.

The goal of General Internal Medicine at MD Anderson is to provide an umbrella of care for these other concerns, known as comorbidities.

As Carmen Escalante, M.D., points out, “When cancer patients present with these various conditions, our team of general internists is there.”

When she joined MD Anderson in 1988, the concept of having general internists in a cancer center was new. She was only the second one hired. Today, as professor and chair of the department, she oversees a faculty of 33, with more coming.

While these doctors practice general medicine, they also have sub-specialties. They are nephrologists, rheumatologists, hospitalists, geriatricians and the list goes on.

“We offer services from seeing patients with a suspicion of cancer to cancer patients with fatigue or needing acute inpatient care,” she says. “We’re involved with patients at all stages of disease and interface with physicians across the institution, addressing comorbidities that need managing. We can do this because as general internists, we have the knowledge to handle diverse health issues.”

### Research and education integral

“We also conduct research that’s patient-centered and helps patients and doctors make decisions about what treatments may work best for individual patients,” says Maria Suarez-Almazor, M.D., Ph.D., professor in the department. “We take into account the potential benefits and harms of interventions, while considering the patients’ preferences.

“Our second goal is to train young investigators and physicians on how to apply and develop methods for research that take into account what matters most to patients, and that are robust and credible.”

### A snapshot of MD Anderson internists

Escalante emphasizes that the center has a long-standing reputation for successful clinical programs, offering quality care to cancer patients. It has also rapidly established productive and credible departmental research while building a legacy that strives for excellence.

### On the following pages, learn about a few of the services offered in General Internal Medicine:

*Mary Ann Weiser Suspicion of Cancer Clinic*

*Hospitalist Care Service*

*Internal Medicine Perioperative Assessment Center*

*Cancer-Related Fatigue Clinic*

*Geriatrics Clinic*

*Rheumatology and Clinical Immunology*





# A front door to answers

By Sandi Stromberg

## Mary Ann Weiser Suspicion of Cancer Clinic

While the X-ray showed a mass on Kenneth Cook's lung, his community doctor was unsure of the diagnosis. That's when Cook's daughter, Brenda, stepped in. She'd worked at MD Anderson early in her career as a pharmacist. Her mother had been treated for stomach cancer at the institution. She knew it was the only place to go.

Fortunately, in the process she found MD Anderson's Mary Ann Weiser Suspicion of Cancer Clinic, the legacy of Mary Ann Weiser, M.D., a dedicated clinician who died of metastatic colon cancer in 2006.

Carmen Escalante, M.D., professor and chair of General Internal Medicine, remembers the day Weiser came into her office. "She said, 'There's a problem. Many patients have cancer, but there's no way they can come to MD Anderson without a diagnosis. I want to learn to do this.' So she started the clinic on her own with few resources and built it into what it is today."

"This has become an important patient service," says John Patlan, M.D., associate professor in the department and director of the clinic since 2008. "With the patient volume having doubled in the past five years, I'm now in the clinic five days a week and gladly welcome another general internist and nurse practitioner this fall."



**A veteran of World War II, Kenneth Cook entered MD Anderson through the Suspicion of Cancer Clinic.**



## Giving illness a name

"The beginning of the cancer journey is the hardest phase of illness," he says. "People can deal with adversity better than uncertainty. We try to help patients have a diagnosis and a plan. They can cope better when they know what they have and what to expect. Also, we're an important point of access to care. Patients can often be seen the same day or the day after they call."

While he's a general internist, he says he's learned a lot about oncology in his nine and one-half years at the institution. "In addition, I can spend more time with patients than a community doctor or a specialist."

In the case of Cook, a diagnosis of stage 4 lung cancer brought him under the care of Frank Fossella, M.D., professor in Thoracic/Head and Neck Medical Oncology. Cook agreed to a biopsy to determine if he carried a certain abnormal gene that would suggest the benefits of a particular drug. When it was found he didn't, he was moved under the care of Marieberta Vidal, M.D., assistant professor in Palliative Care and Rehabilitation Medicine.

With a diagnosis and his side effects under control, Cook took off for one last visit to his Arkansas hometown. That gave the man — who'd worked more than 30 years for Monsanto Oil and Chemical Company, rising from field worker to accountant with a degree in economics — time to visit with his brother, sister and childhood neighbors. And for one last time, he could stand in front of the stone World War II Memorial that bears his name.

**John Patlan, M.D., directs the clinic and helps patients overcome the unknown by getting a diagnosis and a treatment plan.**

# With longer lives come complications

By Mary Brolley

Although most cancer treatment occurs in an outpatient setting, sometimes it's an inside job. Cancer patients can require hospitalization for a variety of reasons.

They may be related to complications caused by comorbidities — health conditions like diabetes or high blood pressure that may complicate treatment and recovery — or to the effects of long-ago cancer treatments.

A growing medical specialty aims to meet the demand for skilled care for these acutely ill patients in the hospital. Called hospitalists, these physicians are experts in providing treatment in a multidisciplinary setting, liaising with specialists as needed, and managing comorbidities and complications of therapy and the disease process.

Norman Brito-Dellan, M.D., assistant professor, is one of MD Anderson's nine hospitalists. The explosion in demand for this specialty is driven by a simple and wonderful fact, he says.

"Cancer patients are living longer. Targeted therapies are effective, and even those with metastatic disease have added years to their lives," he says. "This is a great thing. But with longer lives come unique complications."

There may be consequences of treatment — past exposure to chemotherapy, radiation and more. Hospitalists are well suited to treating these late effects in acutely ill patients in the hospital. They work cooperatively with supervising oncologists and return patients to their care when the acute issues are resolved.

**Hospitalist  
Care Service**

## Split schedule allows for intensive patient care, research

Brito-Dellan came to MD Anderson in 2011 from Intermountain Healthcare in Utah, where he also practiced as a hospitalist. He relishes the demanding pace of the seven-days-on/seven-days-off schedule. His clinical research — on improving the health and quality of life for those with advanced cancer — is conducted on the "off" weeks.

He wouldn't have it any other way.

"It's a very interesting patient population," he says. "For each type of cancer, there may be some distinctive, associated comorbidities. For example, patients with lung cancer may present with acute exacerbations of chronic bronchitis, repeated lung infections and so forth."

Another research focus is standardizing insulin management among inpatients, most with advanced cancer.

"It leads to better outcomes — fewer complications, improved healing, less infection and reduced mortality."

His seven-days-on rotations allow him to really connect with patients and their loved ones, he says. "I love caring for these patients. I learn a lot from them. At some of the worst moments of their lives, they're inspiring. It's something you don't get in other places."

And how does he cope with his stressful schedule? "I run," he says. "I ran a marathon last year."



**Norman Brito-Dellan, M.D., is one of nine hospitalists at MD Anderson.**



# Understanding complications in the midst of complexity

By Sandi Stromberg

Sunil Sahai, M.D., has dedicated his career to assessing and improving patients' chances of surviving surgery. He wants the patient's surgical course to be free of as many avoidable hurdles as possible.

"The challenge has been that some patients suffer complications in the post-operative period because they have medical comorbidities that haven't been addressed prior to the surgery," says the associate professor in General Internal Medicine and director of MD Anderson's Internal Medicine Perioperative Assessment Center (IMPAC).

The IMPAC clinic assesses a patient's risk of complications for surgery — comorbidities often forgotten in the face of cancer's complexities — and takes the necessary precautions before he or she gets on the operating table. This medical optimization of the patient before surgery is done systematically and based on evidence.

## A service surgeons appreciate

"We frequently operate on patients who are considered high risk due to the complexity of their surgery, their medical risk factors, or both," says Randal Weber, M.D., professor and chair of Head and Neck Surgery. "Poorly controlled or unrecognized medical conditions that are not appropriately managed preoperatively can lead to a poor outcome for the patient.

"Multidisciplinary care allows us to achieve optimum outcomes," he adds. "We work closely with our colleagues from IMPAC, who thoroughly evaluate our patients before surgery."

Jason Fleming, M.D., professor in Surgical Oncology and specialist in pancreatic cancer, agrees, "IMPAC has been an extremely valuable resource for determining risk and ensuring comorbidities are accounted for. Ultimately, it allows us to perform personalized, safe and effective surgery."

## Compiling each patient's medical history

While Sahai is the only physician dedicated to the center, the other internists in the department rotate through; there are generally two physicians and an advanced practice nurse on duty each day.

The IMPAC service operates as a "center within the center," staffed with two nurses and two patient services coordinators dedicated to the clinic. The IMPAC team searches records, contacts community doctors and puts together the most accurate and comprehensive medical history possible. Then, they coordinate medically complex patients with the surgery and anesthesia teams.

"We see about 20% to 25% of patients going for surgery or close to 6,000 patients a year," Sahai says. "Some patients don't need to be seen by us because they have few medical issues, and, in general, the better a patient's physical condition, the better the potential for successful surgery without complications.

"The best news is that due to the time we can spend with patients before surgery, the less time they spend in the post-operative setting, dealing with medical complications that could have been avoided, allowing them time to heal and focus on their recovery from cancer," he says.

**Sunil Sahai, M.D., addresses patients' comorbidities before surgery to ensure the best possible outcomes.**

Internal Medicine  
Perioperative  
Assessment Center



# The tiredness that doesn't take a break

By Sandi Stromberg with Andrew Walmsley

When Dolly Sumrow started her cancer treatment, she lost every ounce of energy. Finding MD Anderson's Cancer-Related Fatigue Clinic turned out to be her salvation.

"The difference in my life was like night and day," she says. "The counseling helped me understand how to have the energy I needed to regain my 'normal' routine. In fact, I feel so much better that I almost forget about treatment."

Opened in 1998, the clinic helps patients deal with fatigue, the most common symptom of cancer and cancer treatment. An integrated team of physicians, nurse practitioners and nurse clinicians helps patients find the coping mechanisms that work best for them. For Sumrow, it's turned out to be a combination of the drug Ritalin and exercise, including most recently, water aerobics.

## Some have it, some don't

"We think it may be possible that some people have a genetic predisposition to fatigue, but we don't understand the exact physiology of it. It's what we call a non-specific symptom," says Carmen Escalante, M.D., professor and chair of General Internal Medicine, who has 25 years of experience in this field. "That means it's not like sleep disturbance, pain, hypothyroidism or hypertension. It's difficult to deal with, especially if a patient is expected to go back to work and can't."

Over the years, Escalante and her colleagues have studied exercise, stimulants like Ritalin and educating patients about behaviors that may help reduce fatigue. Limiting naps, avoiding alcohol, caffeine, chocolate and nicotine in the evening, and having a regular sleep schedule are a few other coping mechanisms they recommend.

Most important, Escalante says, is that patients talk with their doctors about their fatigue. Many people don't report symptoms because they think they aren't important. That can have a serious impact on quality of life, as well as physical symptoms.

For Mark Navarro, the diagnosis of multiple myeloma came so late that he had to learn to walk again to be a candidate for a stem cell transplant. But he wasn't prepared for the fatigue that came with the procedure.

Fortunately, a low dose of Ritalin, walking and coaching his daughter's volleyball team have helped immensely. And every Monday, Wednesday and Friday, he can be found on the court at his local YMCA, playing pickle-ball, an increasingly popular racket sport that's a cross between badminton, tennis and ping-pong.

"I have to watch not to overexert myself and run out of energy," he says, "but I love playing with my regular buddies. Life is good, but living it is the best."

**Cancer-Related  
Fatigue Clinic**



**For Mark Navarro (left), being seen in the fatigue clinic and working with Carmen Escalante, M.D., have significantly improved his quality of life.**

# Tailored care for older patients

By Mary Brolley

“Quality of life” might be hard to define, but for MD Anderson’s two practicing geriatricians, guarding and protecting it informs everything they do.

Geriatricians are physicians trained in family practice or internal medicine, who are then trained and board-certified in geriatrics to care for adults 65 and older. Holly Holmes, M.D., and Beatrice Edwards, M.D., both associate professors in the department, specialize in the care of cancer patients in active treatment.

They believe patients and their loved ones shouldn’t plan for survival without considering how treatment might affect their quality of life. This is especially true for frail elders, who may be significantly affected by certain side effects of surgery, chemotherapy, radiation and other cancer treatments. They may be on many medications or dealing with bone loss, cognitive loss, dementia or depression.

Both Edwards and Holmes conduct the Comprehensive Geriatric Assessment with their patients. This is a cognitive, psychological, nutritional, social and functional evaluation that helps in two ways: It allows physicians to determine which patients can have better outcomes with cancer therapy; and it allows geriatricians to tailor an individualized care plan for those beginning cancer treatment.

Although both want to help their patients remain as functional and independent as possible, each has expertise in a field of research crucial to an elder’s quality of life.

Holmes is a former pharmacist whose research focuses on polypharmacy (the interaction of medications) and overmedication.

“Older people take a lot of medications, and we need to find ways to prevent the harms of overmedication during cancer care,” she says.

## Understanding bone health essential

Edwards’ research concerns bone health in cancer survivors. She knows that the health of a person’s bones affects balance, strength and the ability to remain independent.

She says targeted cancer therapies like tamoxifen, aromatase inhibitors and androgen deprivation increase patients’ risk of developing osteoporosis. This condition makes people more susceptible to serious fractures of the hip, spine and axial areas, such as wrists and ankles.

Edwards is also part of the Rolanette and Berdon Lawrence Bone Disease Program of Texas, a collaboration of Baylor College of Medicine and MD Anderson that focuses on treating complex bone disorders. The program brings together internists, endocrinologists, rheumatologists and others to do translational research on safeguarding patients from fractures.

“Cancer ages you before your time,” Edwards says. “We want to stop the disability cascade.”

In our rapidly aging society, it’s clear that cancer among elders — and the difficult treatment decisions that follow — is a growing problem. But Edwards and Holmes try not to get overwhelmed by the demographic trends that show an explosion in the need for geriatricians.

They’re busy caring for patients, doing research and educating oncologists and fellow primary care doctors on the need to tread carefully when making treatment decisions for an aging population.

## Geriatrics Clinic



**Geriatricians Holly Holmes, M.D. (left), and Beatrice Edwards, M.D., both conduct comprehensive assessments with their patients. Each physician also has a sub-specialty that enhances the clinic’s services.**



# When joints, tendons and bones creak

By David Berkowitz

Ever wake up in the middle of the night with an extreme burning sensation in your big toe?

Did it feel so swollen and tender that even the weight of your bed sheet was too much to take?

Gout can be debilitating for the healthiest of people. But for those already dealing with cancer treatment and its often challenging side effects, this and other forms of arthritis may test their powers of coping both physically and mentally.

## An eye on medications

There are more than 100 disorders that typically affect joints, tendons, ligaments, bones and muscles, which fall into the categories of arthritis or rheumatic diseases. Some of these may also involve internal organs.

A team of MD Anderson experts in Rheumatology and Clinical Immunology help address these conditions. The goal is to manage the comorbidities and ensure the best overall quality of life for patients.

“Our main concern is that patients receive medical treatment for these disorders that’s compatible with their cancer treatment and doesn’t place them at risk for side effects from multiple medications,” says Maria Suarez-Almazor, M.D., Ph.D., professor and chief of Rheumatology and Clinical Immunology.

## A range of issues

Suarez-Almazor is one of three full-time rheumatologists who see patients in MD Anderson’s outpatient clinic and in the hospital to address a range of issues, including:

- Complications from treatments, such as gout, osteoporosis or infections to joints
- Managing other rheumatic disorders, like arthritis or lupus
- Treating local problems, such as rotator cuff tendinitis or carpal tunnel syndrome

“We help diagnose diseases by aspirating fluid into swollen joints to check for infection and by performing imaging with ultrasound, which can be done in the clinic so it’s easier for the patient,” Suarez-Almazor says. “Ultrasound can also guide when we give steroid injections to treat arthritis or tendinitis.”

The team’s allergy and immunology clinic provides diagnosis and treatment for allergic and hypersensitivity reactions related to drugs or other allergens, for immunodeficiencies caused by chemotherapy and for autoimmune disorders.

Normally, the immune system’s white blood cells help protect the body from harmful substances called antigens. In patients with an autoimmune disorder, the immune system can’t tell the difference between healthy body tissue and antigens. The result is an immune response that destroys normal body tissues.

Through their research, Suarez-Almazor and her team hope to find other more effective interventions to relieve the comorbidities that affect the joints, tendons, ligaments, bones and muscles — and continue to improve patients’ quality of life.



**Maria Suarez-Almazor, M.D., Ph.D. (left), professor, discusses research protocols with Jean Tayar, M.D. (center), assistant professor, and Huifang Lu, M.D., Ph.D., associate professor. The three work together in Rheumatology and Clinical Immunology, a section of General Internal Medicine.**

**Rheumatology  
and Clinical  
Immunology**

# Seed, soil and metastasis

## Looking beyond the cancer cell

By Hilary Graham

“When a plant goes to seed, its seeds are carried in all directions; but they can only live and grow if they fall on congenial soil. ... While many researchers have been studying ‘the seeds,’ the properties of ‘the soils’ may reveal valuable insights into the metastatic peculiarities of cancer cases.”

— Stephen Paget – 1889

**B**efore physician-scientists had access to state of the art technology, keen observations formed sound hypotheses. Stephen Paget, an English surgeon and pathologist, was the first to document that metastasis did not occur randomly. Metastasis, the spread of primary tumor cells to a secondary organ, is responsible for approximately 90% of cancer deaths.



Upon review of 735 autopsy reports of women who died from breast cancer, Paget found that breast cancer reliably metastasized to the visceral organs and bones. His study — published in the very first issue of *The Lancet*, one of the most respected medical journals — demonstrated that metastases only develop when the seed and soil are compatible.

Paget’s theory lay dormant until challenged in 1928 by James Ewing, an American pathologist. Ewing hypothesized that cancer spreads by purely mechanical factors that are a result of the circulatory system. Ewing’s theory remained the predominant explanation for more than 50 years, until 1984, when it was disproven.

### Biology is never random

Nearly a century after Paget put forth his hypothesis, it finally fell on fertile ground with Isaiah Fidler, D.V.M., Ph.D. Trained as a veterinary surgical oncologist, Fidler later specialized in pathology and became interested in the process of metastasis. While his mentor tried to dissuade him from studying what was then considered a random process driven by anarchy, Fidler was not deterred.

Instead, he dedicated his career to unraveling the complexities of metastasis. Earlier this year, he was awarded the Medal of Honor in Basic Science Research by the American Cancer Society, one of the most prestigious recognitions in the cancer research community.

Fidler’s seminal studies demonstrated that tumors are composed of heterogeneous cell populations and that metastases are non-random biologic events whose outcome depends on the interaction between unique tumor cells with unique organ microenvironments. By uncovering the complex workings of these biological processes, he showed that they are not random, but that we simply fail to adequately understand them.



**Isaiah Fidler, D.V.M., Ph.D., a pioneer in cancer metastasis, has had a storied career at MD Anderson, which spans more than three decades. This year, he was honored by the American Cancer Society with the Medal of Honor for Basic Science Research, one of the most prestigious awards in the cancer research community.**

### **The seeds**

To assure survival, a plant sends out thousands of seeds in the hope that one fit seed will fall on fertile soil and germinate. However, not all seeds are created equal. This is known as heterogeneity.

Similar to plants, tumors produce an overabundance of seeds, shedding approximately four million cells per gram of tumor each day. Despite this, very few tumor cells ever succeed in colonizing new areas of the body.

Fidler set out to determine how cancer cells are disseminated in the body and how many survive. When radio-labeled melanoma cells were injected into mice, he found that only 0.01% of the cells survived and went on to form metastases. Additionally, while the radio-labeled cells reached every organ, they only formed metastases in the lung.

Wanting to understand what allowed the cells to differentially survive and grow, Fidler took metastatic tumors from the lung and isolated the cells, then re-introduced them into mice. This time 1% to 2% of the cells survived, demonstrating that metastatic cells can be selected for, but they only have a proclivity to grow in select tissues.

### **The soil**

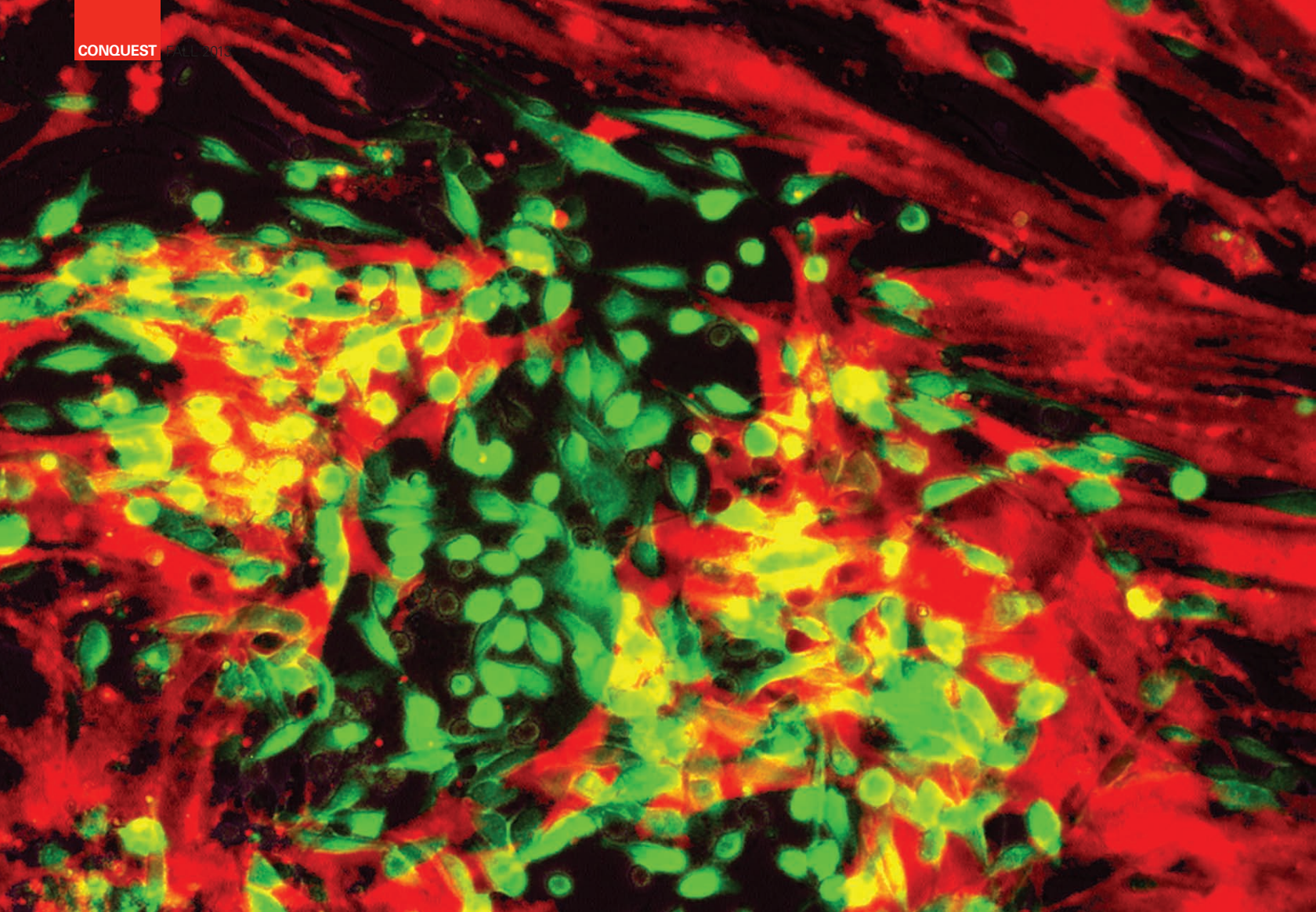
Clearly some organs are receptive to metastasis, and some are not. Considering Paget's theory, if the most fit seed falls on unfertile soil, germination will not occur. But does that analogy also hold true for tumor cells in humans?

To determine the role of soil, now known as the host microenvironment, Fidler and his postdoctoral fellow at the time, Ian Hart, Ph.D., currently at the Barts Cancer Institute, University of London, set out to perform the definitive experiment.

They implanted lung and kidney tissue into the muscle of a mouse and injected melanoma cells intravenously. Their hypothesis: If blood flow was the sole driver of metastasis, then the implanted tissues would have an equal likelihood of metastasizing. If, instead, the host environment influenced metastasis, then the actual lung and the implanted lung tissue would have the same likelihood of metastasizing.

Again they radio-labeled the melanoma cells. This demonstrated that the same number of cells reached the implanted lung and kidney tissues. However, metastases only grew in the lung and the implanted lung tissue. This finding conclusively demonstrated that in the process of metastasis the soil of the host microenvironment is just as important as the seed of the tumor cell.





To better understand the functional role of specific cells in the tumor microenvironment, Valerie LeBleu, Ph.D., and Raghu Kalluri, M.D., Ph.D., fluorescently tagged breast cancer cells in green and smooth muscle actin cells in red. When they overlap, they turn yellow.

### Seed and soil go by many names today

Fast-forward nearly 35 years and tumor microenvironment is a field of intense study.

Because successful metastasis requires many steps, which requires factors from both host and tumor, many disciplines outside traditional realms of cancer biology are contributing to the collective understanding of the process. Subsequently, many terms are used to describe the seed and soil of Paget's day.

Seeds are known as stem cells, progenitor cells, metastatic cells or metastatic clones.

Soil is known as microenvironment, niche or stroma.

The following four sections highlight just a few different approaches to understanding the tumor microenvironment currently pursued at MD Anderson.

### Delving further into the soil

While Raghu Kalluri, M.D., Ph.D., professor and chair of Cancer Biology, started his career studying the cellular scaffolding of the kidney, his research focus has methodically shifted to examining

other structural components, such as blood vessel formation. He's currently interested in the cellular and non-cellular components of the tumor microenvironment.

It may be surprising for those not familiar with tumor microenvironment to learn that solid tumors are composed of more non-cancerous than cancer cells. For example, pancreatic cancer adenocarcinomas are composed of up to 95% non-cancerous cells.

Clearly, cancer cells depend on the cellular environment to sustain their growth and survival, which raises the question: Are non-cancerous cells unwitting participants or enabling partners? With non-cancerous cells being the major constituents of a tumor, understanding the host microenvironmental contributions (the soil) is critical to tackling this disease.

### A wound that never heals

Unresolved scarring, known as fibrosis, often occurs in the kidney, lung and liver, which leads to irreversible organ damage and eventual failure. Similarly, a tumor can be thought of as a fibrotic organ that contains cancer cells.

Valerie LeBleu, Ph.D., assistant professor in Cancer Biology, studies how fibroblasts and mesenchymal (stromal) cells, which produce the structural components of the fibrotic matrix, replace normal tissue with scar tissue — a process known as fibrotic remodeling. While fibrosis normally occurs in a single organ responding to damage, in cancer multiple sites undergo remodeling, specifically the primary tumor site, as well as all secondary metastatic sites.

By drawing upon knowledge from a seemingly unrelated field, LeBleu is shedding light on how cancer cells co-opt stromal cells to aid in progression and metastasis. Instead of relying on assumptions about the contribution of normal cells, detailed molecular analysis now reveals how normal tissues evolve before, during and after the emergence of metastases. This will open new avenues for the rational design of the next generation of therapeutics.

### Harnessing the immune system

Cancer cells can be thought to resemble virally infected cells in two ways. First, they are technically considered “self” by the immune system (as opposed to bacteria, pollen, cells from another human and other materials considered foreign), as they arise from the body’s own cells — like wolves-in-sheep’s-clothing.

Second, both the originating cell (cancer or virally infected) and healthy host cells are critical for survival. Recent research has also demonstrated that the immune response is often suppressed in the tumor microenvironment. This suppression allows cancer cells to flourish.

John Miller, Ph.D., who trained as a virologist and is now a postdoctoral fellow with Lynda Chin, M.D., professor and chair of Genomic Medicine, is working to understand how cancer cells reprogram the immune system.

Because metastatic tumors are the cause of most cancer deaths, knowing which stromal and immune components alter at fertile secondary sites will provide clues to how the immune system could be reactivated to fight cancer cells.

Miller and Chin are mining genomic data from pre- and post-treatment patient samples to identify immune components that influence disease course in melanoma. With a sense of urgency to bring this to patients, Miller hopes that his work will lead to developing immune-based therapies.

### Modeling the microenvironment

Today, scientists recognize that Paget’s observations were valid and that when developing new treatments for patients, both the seed and the soil should be considered. Yet, many scientific experiments continue to rely on studying cells that are grown in plastic dishes, living conditions that are completely artificial and, therefore, inherently biased.

Taking a new path, Giulio Draetta, M.D., Ph.D., professor in Molecular and Cellular Oncology, is leveraging data from the Cancer

### Cancer type Main sites of metastasis\*

<b>Bladder</b>	Bone, liver, lung
<b>Breast</b>	Bone, brain, liver, lung
<b>Colorectal</b>	Liver, lung, peritoneum
<b>Kidney</b>	Adrenal gland, bone, brain, liver, lung
<b>Lung</b>	Adrenal gland, bone, brain, liver
<b>Melanoma</b>	Bone, brain, liver, lung, skin/muscle
<b>Ovary</b>	Liver, lung, peritoneum
<b>Pancreas</b>	Liver, lung, peritoneum
<b>Prostate</b>	Adrenal gland, bone, liver, lung
<b>Stomach</b>	Liver, lung, peritoneum
<b>Thyroid</b>	Bone, liver, lung
<b>Uterus</b>	Bone, liver, lung, peritoneum, vagina

\*Taken from the National Cancer Institute fact sheet on metastatic cancer.

Genome Atlas to conduct *in vivo* context-specific screens that will identify new genetic elements deregulated in cancer.

Once a promising target is identified, his group performs these screens in the appropriate organ context to validate the target. By directly studying patient tumor tissue samples that often resist standard of care, his research group ensures that research findings are directly applicable to patients, who currently have no therapeutic options.

In collaboration with MD Anderson’s Center for Co-Clinical Trials, they’re also generating new mouse-model systems that carefully control for lineage, genetic and microenvironmental influences. Draetta envisions that in the near future similar analyses will be available for individual patient tumors — making personalized medicine a reality.





**Picture This**

**Children’s Art Project celebrates 40th anniversary**

By William Fitzgerald

**When a small group of volunteers began selling holiday cards inspired by artwork from MD Anderson’s young patients back in 1973, little did they know their efforts would lay the foundation for big things to come.**

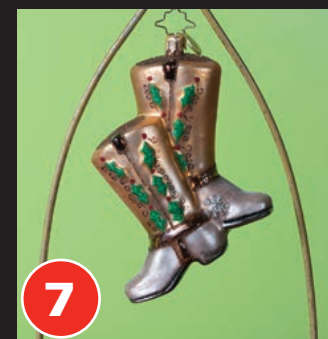
They were the pioneers of what would become the Children’s Art Project (CAP), a year-round program dedicated to bringing the creativity of children to life in gift merchandise, ranging from ornaments to cell phone covers and much more.

“It’s incredible to look at the history of this program and its accomplishments,” says Shannan Murray, CAP’s executive director.

“We’ve given back more than \$30 million, which has allowed us to support numerous programs benefiting the educational and recreational needs of our patients.”

For those in metropolitan Houston, the CAP Boutique in the Uptown Park Shopping Center has become the go-to spot for purchasing the latest gifts. It’s also the best place to get the full CAP experience.





**The Children's Art Project provides an opportunity to support special programs for MD Anderson patients.**

**1. Stationery, \$8-\$16**, is the mainstay of each CAP collection. From greeting cards to photo cards to personalized cards, there's much from which to choose.

**2. Shannan Murray** is the third executive director of the program after joining in 1997. Under her leadership, CAP has expanded and currently sells products in more than 2,100 retail locations in 11 states.

**3. In the background**, CAP intern Katelyn Vonderheide arranges displays.

**4. AmREIT, Gexa Energy and Cooper Industries** have all generously contributed over the years by covering some of the store's operational costs, including rent.

**5. Patients are the core of CAP's mission** and displays proudly inform customers about the children behind the artwork. Pictured here is Bandar Alfadhel, 13, a prolific artist who says the program, "helped me get over the mountain."

**6. Doug Burchfield**, a longtime MD Anderson volunteer and store manager, assists a customer. Last year, CAP volunteers provided nearly 500,000 hours of service, which equates to the work of more than 230 full-time employees.

**7. The Holly Boot Radko Ornament**, \$50, is one of the best-selling pieces in CAP's ever-growing ornament collection. Each is crafted and hand painted in Poland.

**8. Bee Flowers Domino Necklace**, \$28, was created by Kierra Hill, a longtime artist known for her colorful designs. Several other necklaces are also available, and many are based on seasonal themes.

**9. Ties, \$38, come in a variety of designs** and are part of CAP's apparel collection, which also includes scarves, shirts, aprons and more.

**10. The CAP Boutique** is open Monday through Saturday from 10 a.m. to 6 p.m. with extended holiday hours on Sundays from noon to 5 p.m., beginning Oct. 13.

*To learn more about CAP and its products, or to place an order, call 800-231-1580 or visit [www.childrensart.org](http://www.childrensart.org).*



# Brain waves, eating habits and lipids

## Researchers weigh in on obesity

By Katrina Burton

### FOOD ON THE BRAIN

#### Internal mechanisms behind obesity

Has the thought of consuming a bag of chocolate chip cookies or a bag of chips ever hijacked your brain? Well, you might be partially right in that assessment, according to a theory that has prompted an MD Anderson cancer prevention study.

Susan Schembre, Ph.D., and Francesco Versace, Ph.D., assistant professors in Behavioral Science at MD Anderson, have teamed up to explore whether excessive eating is linked to neurological mechanisms — brain-reward responses — similar to those associated with substance-use disorders. They're guided by recent smoking research in Versace's lab. Findings there have shown that certain patterns of brain responses to emotional cues or rewards may be key to understanding smoking behavior, cessation and relapse.

In other words, neurological responses may trigger something in our brain that's responsible for why we overeat. Schembre and her group are using the drug-addiction framework to investigate cognitive and psychological factors that promote excessive weight gain.

#### Getting to the why of weight gain

"There's plenty of research on diet and physical activity as an important part of losing and maintaining weight loss," Schembre says. "There's less research investigating the reasons why some people overeat and gain or regain an excessive amount of weight."

For the majority of overweight people, dieting is ineffective. In fact, 80% to 90% of people who lose weight cannot maintain any significant loss. While research shows that a combination of healthy eating and physical activity is the way to weight loss, for most people, sustaining these behaviors can be difficult, leading to weight regain.

Schembre's new research study, Project Weight, is investigating whether there are differences in brain-reward responses to images of food similar to other emotionally pleasant images among three groups: obese people, obese people in a weight-loss program and lean people with no prior weight issues.

"Our goal is to find a new way to conceptualize strategies and interventions to help people make behavioral changes and live a healthy life at a healthy weight without taking part in popular dieting trends or drastic measures like surgery," Schembre says.

## The facts are daunting.

More than one-third of U.S. adults are obese with medical costs of \$147 billion in 2008 alone.

Yet, according to the Centers for Disease Control and Prevention, obesity-related conditions — heart disease, stroke, type 2 diabetes and certain types of cancer — cause deaths that might have been prevented.

At MD Anderson, the condition, increasingly referred to as a disease itself, is being addressed on several fronts by behavioral scientists, epidemiologists and clinical cancer prevention experts.



**Top: Danika Dirba (left), senior behavioral science lab tech, and Susan Schembre, Ph.D., assistant professor in Behavioral Science, view the brain waves of a study participant as she looks at a tempting image of donuts. Bottom: Ivan Uray, M.D., Ph.D., assistant professor in Clinical Cancer Prevention, studies the intersection of obesity, diabetes and cancer.**

## LIPIDOMICS: AN EMERGING FIELD

### Where obesity, diabetes and cancer meet

Lipids are a large and diverse group of naturally occurring molecules known to most of us as cholesterol, fatty acids, triglycerides, etc.

For decades, researchers have studied the complex process of lipid metabolism — the uptake of processing, storing and disposing of these molecules — because they have very fundamental functions not only in energy storage, but also are very important mediators of various events between cells and intercellular activity. In addition to playing a role in diabetes and obesity, they're now being linked to cancer.

At MD Anderson, Ivan Uray, M.D., Ph.D., assistant professor in Clinical Cancer Prevention, is focusing on the fast-growing field of lipidomics — the study of cellular lipids and lipid-mediated signaling pathways in biological systems — to investigate a lipogenic enzyme that, as part of a maladaptive process, may promote cancer development.

“It’s important that we understand this underserved area of research because obesity, diabetes and insulin resistance are risk factors for breast cancer,” he says. “On the other hand, it’s difficult to establish reliable, accurate methods to answer scientific questions pertaining to the study of lipids because they’re not water soluble and, therefore, cannot easily be studied by the same methods as proteins and sugars.”

He and his team are studying diacylglycerol acyl-transferase (DGAT1), a lipogenic enzyme responsible for making complex lipids for storage, which is amplified in 5% to 20% of cancer cases.

“Our research is unique because this enzyme has never been studied in cancer,” Uray says.

In a grant recently funded by the National Cancer Institute, he and his team are investigating the potential of suppressing DGAT1 activity to prevent or delay breast cancer.

The other important aspect of studying this enzyme is that drugs have already been developed and are currently being clinically tested as a treatment for type II diabetes and obesity. In preclinical studies, data showed that mice lacking DGAT1 were leaner, had higher insulin sensitivity and lived longer.

“If we can find a way to better control obesity and diabetes, we can also reduce the risk of cancer,” Uray says.

## NO MAGIC FOODS

### Understanding nutrition and the causes of cancer

The role diet plays in a person’s cancer risk has been the subject of debate for many years, as people seek that one “super” food that might prevent cancer.

“The reality is that there’s not one ‘magic bullet’ food or nutrient that will prevent cancer,” says Carrie Daniel-MacDougall, Ph.D., assistant professor in Epidemiology at MD Anderson. “Nearly every large clinical trial testing a vitamin or supplement has been disappointing. Nutrition is a science. We have to remember to think critically and not just follow popular trends.”

As a nutritional epidemiologist, Daniel’s research has traditionally focused on the role diet plays in cancer development and prevention.

“The problem with cancer is that it’s not one disease,” Daniel says. “What we find for one type of cancer may not translate to another.”

### Cancer risk lowered by small changes in habits

With the staggering public health problem of obesity now ranked as the primary cause of cancer in non-smokers, she believes we can learn more from a broader approach targeting obesity and related conditions, like diabetes and hypertension, that are also linked to some cancers.

“Epidemiology has been integral in providing research to support the promise that cancer risk can be lowered by making small, positive changes to everyday habits,” she says. “We need to continue to build the scientific and mechanistic evidence for obesity and cancer, while searching for links to modifiable risk factors, like diet and physical activity.”

Daniel was the lead investigator on the largest prospective analysis to date of the relationship between fiber intake and renal cell carcinoma, the most common type of kidney cancer. In this study, she showed that high dietary fiber intake from fiber-rich plant foods — like beans or legumes, whole grains and cruciferous vegetables — was associated with a 20% reduction in the risk of developing kidney cancer. The study, published in the American Journal of Clinical Nutrition, followed the dietary and lifestyle habits of 500,000 healthy men and women between the ages of 50 and 71 over 10 years for cancer incidence or development.

This type of research is a step toward educating people on choosing the right foods to help fight the internal mechanisms that may contribute to obesity and cancer.

Daniel is also studying the vast gut microbiome. “We know that many different bacteria live within the digestive tract and affect a person’s health. I’m interested in how these bacteria are shaped by dietary habits and influence the risk of developing obesity and cancer.”



Carrie Daniel-MacDougall, Ph.D.



# The GSBS story: 50 years of educating scientists

## A snapshot of co-leaders' first year

By Sandi Stromberg

In 2012, the presidents of MD Anderson and The University of Texas Health Science Center at Houston (UTHealth) took an unprecedented step that changed a 50-year tradition. They appointed two scientists to lead the Graduate School of Biomedical Sciences (GSBS): Michelle Barton, Ph.D., from MD Anderson, and Michael Blackburn, Ph.D., from UTHealth.

Barton and Blackburn had been active in GSBS for many years — teaching in their areas of expertise, training students in their labs, serving on committees and assuming other leadership roles — before they became its joint leaders. And both are experts in biochemistry and molecular biology: Barton and her lab pursuing new findings in epigenetics and breast cancer (see story on page 24), Blackburn studying lung diseases.

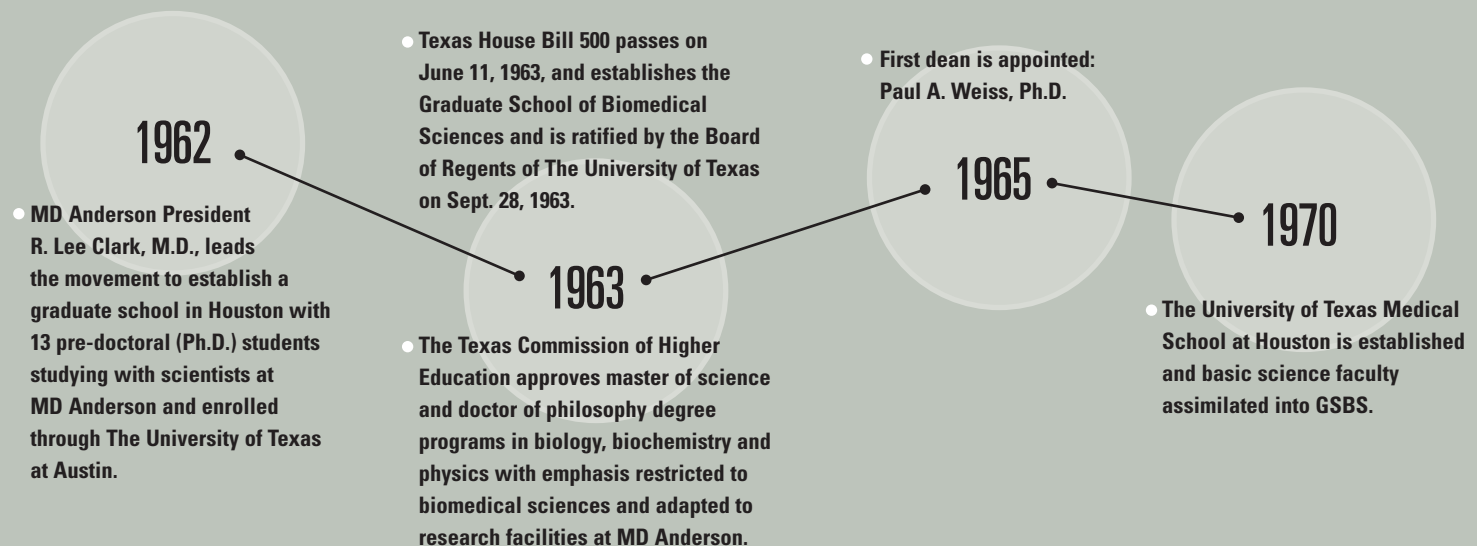
It's been an inspired move that has set the graduate school, a partnership between the two institutions, on an enhanced path as it celebrates its 50th anniversary this autumn. MD Anderson President Ronald DePinho, M.D., and UTHealth President Giuseppe Colasurdo, M.D., were both on hand for the kick-off reception on Oct. 3. An alumni reunion is scheduled for November, and there will be various other events throughout the year.

• **What has been accomplished in your first year in this position?**

**Blackburn:** We've accomplished quite a lot. A few examples include enhanced recruitment and admissions practices and outcomes; the formation of a "boot camp orientation" for new students; and enhanced efforts in career development for our students.

**Barton:** We've been active on many fronts. To mention only a few: The overall quality of our entering Ph.D. class was significantly enhanced. We successfully recruited 27% more top-ranked students than last year. We also facilitated an external review of the graduate school by three national leaders in biomedical graduate education. The written report will help guide strategic planning efforts in admissions and recruitment, curriculum and programs, as well as career development.

### • Historical highlights of the GSBS





**Michael Blackburn, Ph.D., and Michelle Barton, Ph.D., find working together as co-leaders of the Graduate School of Biomedical Sciences a rewarding career move and something to celebrate along with the school's 50th anniversary.**

- **What are your goals for the school?**

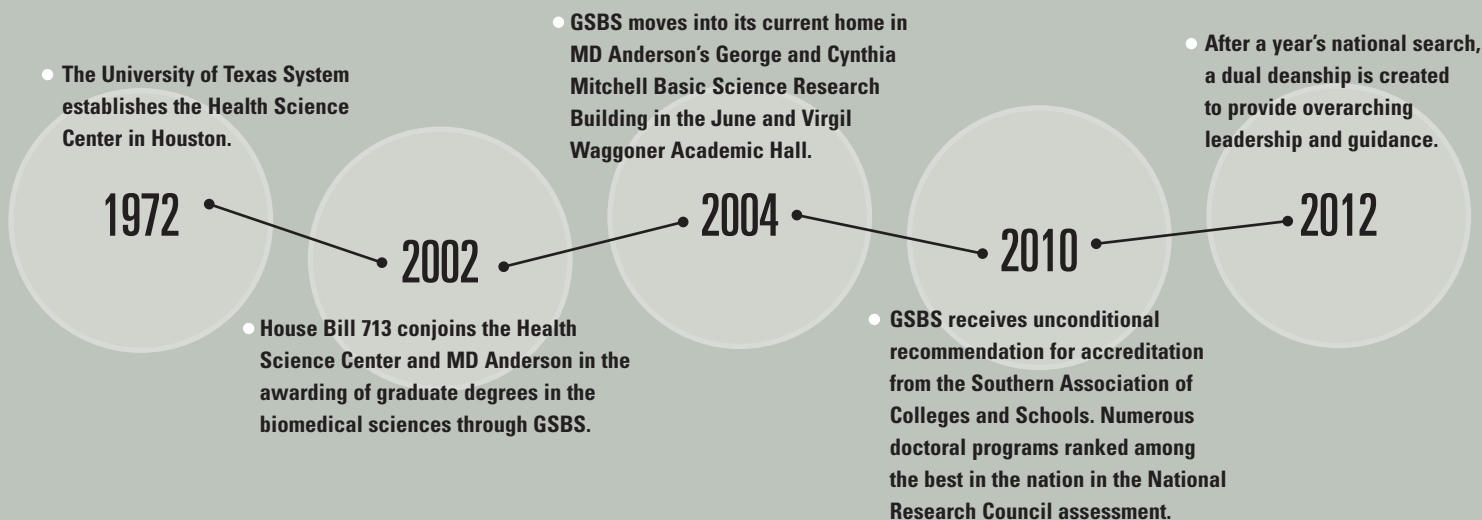
**Barton:** The primary one is to give our students the self-confidence they need to realize the potential each and every one of them has. I know this will help us accomplish our other major goal, which is to broadcast to the world what a fantastic graduate school we have here, the incredible resources we have and the unique opportunities we offer.

**Blackburn:** The broad goals for the school include enhancing the overall quality of the education, increasing its visibility in the scientific community and improving ranking among other graduate schools. To help accomplish these goals we're putting in place programs to enhance our recruitment of top students, expose them to innovative curriculum, promote critical thinking and communication, and facilitate their research training in the laboratories of our outstanding faculty.

- **How does it feel to be sharing this leadership position as the school reaches its 50th anniversary?**

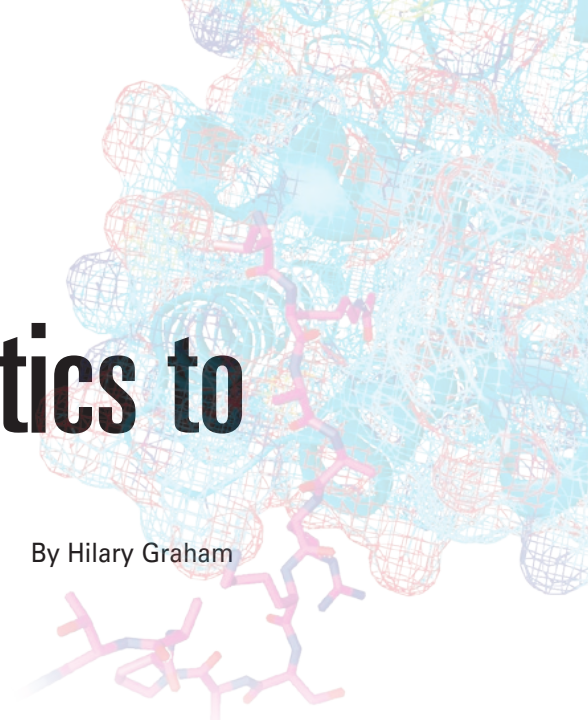
**Barton:** To share this with Dr. Blackburn is the best way to tackle the challenges of this position. We've been able to work in synergy and complement each other's strengths. It's great that it occurs at the time of our 50th anniversary.

**Blackburn:** Working with Dr. Barton is one of the biggest wins of our first year, and it's fun to celebrate the anniversary together. We've developed a new tag line for the school, "Synergy in Science." It was Dr. Barton's idea, and it really captures what we're promoting. We're unique in that we serve two institutions, which together excel in research efforts that target not only cancer, but nearly every common disease that afflicts our society. The opportunity this provides our students is amazing and gives us much to celebrate.



# Understanding epigenetics to develop new therapies

By Hilary Graham



Some might call it fate. Three scientists who started their careers in different parts of the world and come from different scientific disciplines now work together at MD Anderson to develop new treatments for patients.

Philip Jones, Ph.D., a medicinal chemist originally from England, and Jannik Andersen, Ph.D., a biologist originally from Denmark, are both drug discovery scientists who spent time at the pharmaceutical giant, Merck and Co., while Michelle Barton, Ph.D., a professor in Biochemistry and Molecular Biology, is originally from Illinois and has spent the past 13 years at MD Anderson.

When Jones and Andersen moved from Boston to join the Institute for Applied Cancer Science (IACS) in 2011, they were excited to meet Barton, whose research had linked a novel epigenetic protein to breast cancer. This work, which was published in the prestigious journal *Nature*, included an analysis by Mien-Chie Hung, Ph.D., vice president for Basic Research and co-leader of the Breast and Ovarian Moon Shot.

The study characterized the mode of action of a novel bromodomain-containing protein, called TRIM24, and showed that overexpression of this protein correlates with a poor prognosis for breast cancer patients.

## The histone code

When genomic DNA is packed into the nucleus of a cell, it's first wrapped around a core of histone proteins, which condenses the DNA into chromatin structures — like thread wrapped around a spool. Several families of enzymes then act in concert to add or remove small chemical marks that modify the histones. These marks have evolved into a sophisticated language known as the “histone code.”

In contrast to DNA mutations, these marks are reversible (i.e. they can be written and erased), and the study of these marks is known as epigenetics. These modifications act as “zip codes” to recruit specific enzymes to the DNA, thereby controlling gene expression and, in the case of cancer, promoting aberrant cell growth. TRIM24 is one such protein that binds to these chemical marks and helps to read the histone code.

Promising new drugs that prevent the binding of specific epigenetic reader proteins to histones are already in early clinical development. Barton's data suggests that inhibiting TRIM24 with a small molecule drug might benefit breast cancer patients.

## Formation of a drug discovery team

Based on the above discovery, Jones and Andersen quickly established a collaboration with Barton and her research group to jump-start a drug discovery program on TRIM24 and other cancer-relevant “reader” proteins. First, they assembled a cross-functional team of scientists from within IACS who have the shared goal of identifying a small molecule that can bind to TRIM24 and inhibit its function in cancer cells, which may ultimately benefit patients as a therapeutic drug.

The project team comprises scientists from multiple disciplines, who work together to design a single molecule with all the characteristics necessary for a new drug to be effective in the clinic.

**The project teams at IACS work to identify drug candidates that selectively kill cancer cells. Via a cross-departmental collaboration, Yanai Zhan (left) and Xi (Thomas) Shi (center), members of Jannik Andersen's biology team, discuss such findings with Srikanth Appikonda, Ph.D., postdoctoral fellow in Michelle Barton's lab and an expert on TRIM24 biochemistry.**





## Working together toward a common goal

To initiate any small-molecule drug discovery program, a suitable screening assay (test) must be established to evaluate small molecules that may bind to and inhibit the protein. This requires an understanding of the underlying biology of the target protein and its role in the disease process.

Fortunately, through some elegant scientific experiments, Barton's group had already defined the specific histone mark that was recognized by TRIM24. These insights allowed the *in vitro* pharmacology group at IACS to quickly establish relevant binding assays. Such tests are conducted rapidly and reproducibly using extensive laboratory robotics.

Medicinal chemists at IACS then began to design and synthesize novel small molecules that bind to pockets on the protein's surface. Close collaborations with structural biologists John Ladbury, Ph.D., and Guillaume Poncet-Montange, Ph.D., professor and instructor in Biochemistry and Molecular Biology respectively, allow the medicinal chemists to get a snapshot of how their small molecules interact with the protein, thereby helping them rationally design the next iteration (see "Revealing structural insights," page 27).

Typically the chemistry team makes 25-50 new molecules each week, which are then tested in the screening assays. When the biological data is returned to the chemists, they seek to understand which features of the molecule improve activity and immediately make more potent versions.

In addition to potency, the medicinal chemistry team must install all the qualities necessary for the compound to be effectively

absorbed and properly distributed in the body and delivered to cancer cells. They also need to avoid its premature elimination from the body by metabolism and excretion. Finally, the team ensures the drug will be safe and well tolerated in humans. To date, the team has generated thousands of related small molecules that are progressively becoming more drug-like.

In parallel, Andersen and his team developed sophisticated novel assays to measure the activity of TRIM24 in cancer cells — showing how this protein enters the nucleus of cancer cells and binds to histones. The small molecules made by the IACS team block this interaction. Currently the project team is working with Barton's group to further understand how and in what specific setting this inhibition can effectively kill cancer cells.

Beyond TRIM24, IACS is also aggressively focusing on other epigenetic proteins that "write" and "erase" the histone marks. These fully integrated projects align cancer biologists and drug discovery scientists at IACS with the world-class clinicians at MD Anderson, working toward the common goal of delivering new effective therapeutics that benefit cancer patients.

## Collaboration and discovery

Beyond the drug discovery effort at IACS, a number of MD Anderson researchers and clinicians are making seminal contributions to the fundamental understanding of the biology of epigenetic regulators, as well as leading clinical trials of newly developed experimental epigenetic therapies.

## Building a community

Sharon Dent, Ph.D., professor and chair of Molecular Carcinogenesis, has played an integral role in building capabilities and recruiting key talent in the epigenetics field to MD Anderson. As director of the Center for Cancer Epigenetics, established in 2007, she's helped foster a vibrant community of epigenetics research. Composed of more than 60 members, the center allows researchers to share unpublished findings and discuss their current studies at bi-monthly meetings and an annual retreat.

The center, which is generously supported by the Duncan Family Foundation and the T.L.L. Temple Foundation, also provides pilot grants, trainee scholarships and research allowances.

Dent is excited to be part of a field that's on the cutting edge of cancer biology, specifically new technologies that are generating comprehensive maps of all epigenetic marks across the genome. This unbiased approach of examining normal cells and tumor cells, as well as cells from early-stage and late-stage disease, is elucidating how the epigenetic landscape changes as a cancer initiates and progresses.

This data will provide a road map of how the epigenome is altered and which factors are critical to driving cancer progression. By looking not only under the lamppost, but also more broadly at the entire landscape, Dent is confident that new targets for drug discovery will be uncovered.



## Expanding the search

Mark Bedford, Ph.D., professor in Molecular Carcinogenesis, works to identify novel epigenetic interactions and their role in disease.

Bedford has developed a technology that immobilizes more than 300 different epigenetic domains on a glass slide. These can be used to identify proteins that interact with the domains, as well as small molecules that may serve to inhibit them. He established the Protein Domain Microarrays Core to provide this technology to other researchers. Using this technology, researchers can identify the molecular interactions of many types of epigenetic readers, which include a variety of epigenetic domains.

Bedford's research program focuses specifically on arginine methylation, one type of epigenetic modification, and the family of enzymes that add this mark — protein arginine methyltransferases. Only recently has this family of enzymes been definitively linked to cancer. Interestingly, they do not appear to be mutated in cancer; instead, an overproduction of these enzymes is often observed in cancer cells. By understanding their cellular roles, Bedford anticipates that new avenues for drug development will become available.

**FDA approved epigenetic-based therapies: Vorinostat (Zolinza) and romidepsin (Istodax) inhibit histone deacetylases, while azacitidine (Vidaza) and decitabine (Dacogen) inhibit DNA methyltransferases — all effective treatments for blood cancers.**



## Revealing structural insights

Structural biologists work at the intersection of biology and chemistry, as they determine the physical structure of proteins. The IACS collaboration with Ladbury and Poncet-Montange has enabled the project to progress rapidly, as they provide critical insights on how IACS' small molecules bind to drug targets.

To determine the structure of a protein, it must first be crystallized, which is no easy task. Often thousands of conditions must be tested before crystals form. These crystals are then soaked with the drug of interest. The samples are then bombarded with high-speed X-rays that give rise to unique diffraction patterns. Sophisticated computer algorithms then allow the three-dimensional protein structure to be solved, thereby revealing how the drug binds (see image right).

Ladbury and Poncet-Montange have solved more than 50 proprietary drug-bound structures to date.

## Epigenetic-based cancer therapies

Hagop Kantarjian, M.D., professor and chair of Leukemia and co-leader of the Leukemia Moon Shot, is leading a clinical trial to investigate the safety and effectiveness of a DNA hypomethylating agent, developed by Astex Pharmaceuticals, in patients with high-risk myelodysplastic syndromes or acute myeloid leukemia.

Currently, there are four available anti-cancer drugs on the market that target two classes of epigenetic regulators (see photo above). A number of leading pharmaceutical and biotechnology companies continue to expand their programs surrounding the development of epigenetic-based therapies. In fact, the next generation of epigenetic cancer drugs promises to be tailored to specific patient populations, based on biomarkers and diagnostic tests.

**John Ladbury, Ph.D., and Guillaume Poncet-Montange, Ph.D., crystallize proteins, such as TRIM24 (green), in complex with small molecules or biological binding partners. In turn, these solved structures guide the chemists in their design of small molecules with improved properties.**





# CANCER BRIEFINGS



## No. 1 again for MD Anderson

For the seventh straight year, MD Anderson has been ranked No. 1 in cancer care by U.S. News and World Report's annual "Best Hospitals" survey. During the past 12 years, the institution has ranked first in cancer care 10 times. Since 1990, when the survey began, it's been listed as one of the top two cancer hospitals in the nation.

Also nationally ranked are three MD Anderson specialties: ear, nose and throat (No. 3), gynecology (No. 6) and urology (No. 43). The institution's orthopedic, neurosurgery, nephrology, psychiatry and geriatrics services were named as "High Performing" specialties.

MD Anderson continues as one of the largest cancer centers in the world, last year serving more than 115,000 people, nearly one-third of them new patients. Many come to the institution seeking the latest therapies, diagnostics, surgical techniques and prevention strategies.

About 8,500 patients were registered on clinical trials exploring new treatments last year, making it home to the largest clinical trials program for cancer in the nation.

## Potential role of neighborhood environment in obesity

Recent findings show that African-American adults living closer to a fast food restaurant have a higher body mass index (BMI) than those who live further away from fast food. Published online in the American Journal of Public Health, the study was led by Lorraine Reitzel, Ph.D., assistant professor in Health Disparities Research at MD Anderson.

Data were collected from a large sample of more than 1,400 African-American adult participants taking part in the Project CHURCH research study, a collaboration between MD Anderson and Windsor Village United Methodist Church in Houston, one of the largest Methodist churches in the United States.

The study controlled for factors that may influence a person's BMI, including:

- Gender and age
- Physical activity
- Individual household income, median neighborhood income
- Income and education
- Partner status and whether there were children in the home
- Employment status
- Residential tenure
- Sedentary behaviors (the amount of time watching television)

Although the study indicated that the relationship between a higher BMI and proximity to fast food was stronger among those of lower incomes, it was still significant in the group with higher incomes. The data also show that every additional mile participants live from the closest fast food restaurant was associated with a 2.4% lower BMI.

"Fast food is specifically designed to be affordable, appealing and convenient," Reitzel says. "People are pressed for time, and they behave in such a way that will cost them the least amount of time to get things done, and this may extend to their food choices." She also notes that those with lower incomes may have less access to transportation to healthier food options.

## Read Conquest on your iPad

The award-winning Conquest magazine, which includes MD Anderson's Annual Report as its winter issue, is now available on Apple's iPad.

The free Conquest app can be downloaded from the iTunes App Store. You can keep as many issues as you'd like on your iPad Newsstand, where they can be viewed at any time.

Each tablet edition features an easy-to-navigate presentation of the latest cancer research, treatment and prevention strategies, innovative patient services and programs, and human interest stories about patients, donors, faculty, staff and volunteers.

In addition to content presented in the print version of Conquest, the iPad edition includes interactive elements such as videos, podcasts, photo galleries, linked resources and more.

To download the app, visit the iTunes App Store and search for "Conquest Magazine." After downloading the app, a free subscription banner will appear. Selecting this option enables you to automatically receive push alerts through Newsstand each time a new issue is published.

For those without an iPad, Conquest is available online at [www.mdanderson.org/conquest](http://www.mdanderson.org/conquest). While there, you can subscribe to receive email alerts when new issues are ready.

Also, you can subscribe to RSS feeds for the latest Conquest content or audio versions of each issue. To subscribe, go to [www.mdanderson.org/publications/rss](http://www.mdanderson.org/publications/rss).

*The free print edition is available by emailing Lany Kimmons at [RLKimmons@mdanderson.org](mailto:RLKimmons@mdanderson.org).*



**Back issues of the Conquest Magazine app are now available. These include Fall 2012, the 2011-2012 Annual Report (winter issue), Spring 2013 and Summer 2013.**

## Abbott acquires MD Anderson technology company

Abbott Laboratories Inc., has agreed to purchase a private company based on technology discovered at MD Anderson for \$310 million. IDEV Technologies Inc., of Webster, Texas, has developed an innovative stent system to treat blockages in blood vessels and the narrowing of bile ducts in the liver. The system may also have broad applications in additional medical markets.

"We're excited about Abbott's acquisition of IDEV Technologies, a company that was founded upon a portfolio of more than 30 technologies developed by MD Anderson," says Chris Capelli, M.D., vice president for Technology Based Ventures at MD Anderson.

The innovative technology uses an interwoven stent design that mimics natural movement, providing greater strength and flexibility than traditional stent designs.

"These properties are particularly important when considering treatment for blockages in the blood vessels in the thigh and knee where rapid and frequent movement occurs with daily activities, such as walking, sitting and standing," Abbott's announcement notes.

"We believe that the transaction represented the culmination of an extremely successful commercialization project for MD Anderson, and the beginning of an exciting new stage of development for our technology," Capelli says.

MD Anderson will continue to receive royalties under its licensing agreements. Such payments help fund research and represent an important revenue stream for the institution.

Signs of Hope | Appearances count

By Gail Goodwin

Distinctive needs, distinctive products

Studies show that feeling good about yourself goes a long way toward keeping a positive attitude during cancer treatment. In turn, a positive attitude often leads to a more positive experience throughout a cancer journey.



Part of staying upbeat is having certain needs met, a fact that Volunteer Services at MD Anderson understood when they opened Appearances in the Lowry and Peggy Mays Clinic. Unique in Houston, the hospital-based specialty shop markets to the distinctive needs of cancer patients.

**Taking measurements**

Breast cancer patients can take advantage of the expertise of the certified mastectomy fitter, Maritza Valero (above), who manages Appearances. Valero began working in the shop as a volunteer and soon found that her passion is fitting patients after breast surgery and making sure they're happy.

Breast prostheses, or breast forms, are used to replace a breast removed during a surgical procedure. The devices offer optimum outcome for a balanced appearance and are available in different shapes and sizes to accommodate various body types, breast shapes, skin tones and surgeries.

Valero, who's certified through the American Board for Certifications in Orthotics, Prosthetics and Pedorthics, works with Kobra Karbalai (far right), another mastectomy fitter. Together, they fit an average of 100 patients each month.

Lee Madray (right), who has clocked more than 1,000 hours in her eight years as a volunteer, stands in front of shelves filled with products designed for cancer patients — from special toothpaste and toothbrushes, creams and lotions, lip balm, hypoallergenic deodorant, sunscreen and shampoos.



For the cancer patients who lose their hair during chemotherapy and/or radiation treatments, there are an array of colorful scarves, hats and turbans.

Other items in the shop include canes, leisure and swimwear, CVC covers and cancer care awareness products, books, cookbooks and journals, as well as inspirational items.







By David Berkowitz

Images on the computer screens may be familiar to Conquest readers. Over the past nine years, Wyatt McSpadden has photographed dozens of MD Anderson patients, caregivers, donors and health care professionals.



**A**s a professional photographer for more than 35 years, Wyatt McSpadden has focused his lens on thousands of subjects — from the down and out, to the high and mighty, and everyone in between.

When he was hired in 2003 to take portraits of cancer survivors for a series of panels in MD Anderson's hallways and waiting areas, little did he realize that he would be capturing his future self.

In August 2011, McSpadden had surgery near his home in Austin, Texas, to remove what was presumed to be a benign tumor on his left parotid (salivary) gland.

His surgeon discovered a poorly differentiated carcinoma that was wrapped around the facial nerve. A partial parotidectomy removed several lymph nodes that were involved, but spared the nerve.

"My cancer was tricky to diagnose because they weren't sure of the primary source of the tumor. My doctor referred me to MD Anderson, where I was diagnosed with lymphoepithelioma," McSpadden says.

To treat the rare cancer, he received a nine-week course of chemotherapy followed by 33 days of targeted radiation on the left side of his face and neck, plus a weekly remedial dose of chemo.

When McSpadden and his wife, Nancy, returned to MD Anderson three months after his final radiation treatment for PET scans and tests, he received great news.

"Our doctors described those scans as 'perfect,' and I continue doing extremely well today," he says.

### Back in the saddle

A native Texan who has contributed to Smithsonian Magazine and done years of work for Texas Monthly magazine, McSpadden has enjoyed what he calls "some remarkable assignments" since completing treatment.

They include a portrait session with country music legend Willie Nelson, a three-day assignment at the historic JA Ranch near his hometown of Amarillo, and taking the cover photo and inside shots for the magazine's June 2013 feature, "The 50 Best BBQ Joints."

But continuing to photograph patients and staff for MD Anderson's Conquest magazine remains near the top of McSpadden's list of favorite projects.

"Navigating the cancer highway has changed my perspective about this work, making my interactions with fellow travelers seem more real and honest," he says. "And my appreciation for MD Anderson and the remarkable people who make it the best cancer hospital in the world is personal and runs deep."

To view samples of Wyatt McSpadden's photographic work, check his website at [www.wyattmcspadden.com](http://www.wyattmcspadden.com).

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**LOCATIONS**

In addition to MD Anderson’s main campus in the Texas Medical Center in Houston, four regional care centers in the greater Houston area (Bay Area, Katy, Sugar Land, The Woodlands) and two research campuses in Bastrop County, Texas, the institution has developed a network of national and international locations.

**MD ANDERSON CANCER NETWORK™**

www.mdanderson.org/cancernetwork

**PARTNER MEMBERS**

- Banner MD Anderson Cancer Center (Gilbert, Ariz.)
- MD Anderson Cancer Center at Cooper (Camden, N.J.)
- MD Anderson Cancer Center Orlando (Orlando, Fla.)

**AFFILIATES**

- MD Anderson Cancer Center Madrid (Madrid, Spain)
- MD Anderson Radiation Treatment Center at American Hospital (Istanbul, Turkey)
- MD Anderson Radiation Treatment Center at Presbyterian Kaseman Hospital (Albuquerque, N.M.)

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For information on patient services at MD Anderson, call askMDAnderson at 877-632-6789, or log on to www.mdanderson.org/ask.

