

# CONQUEST

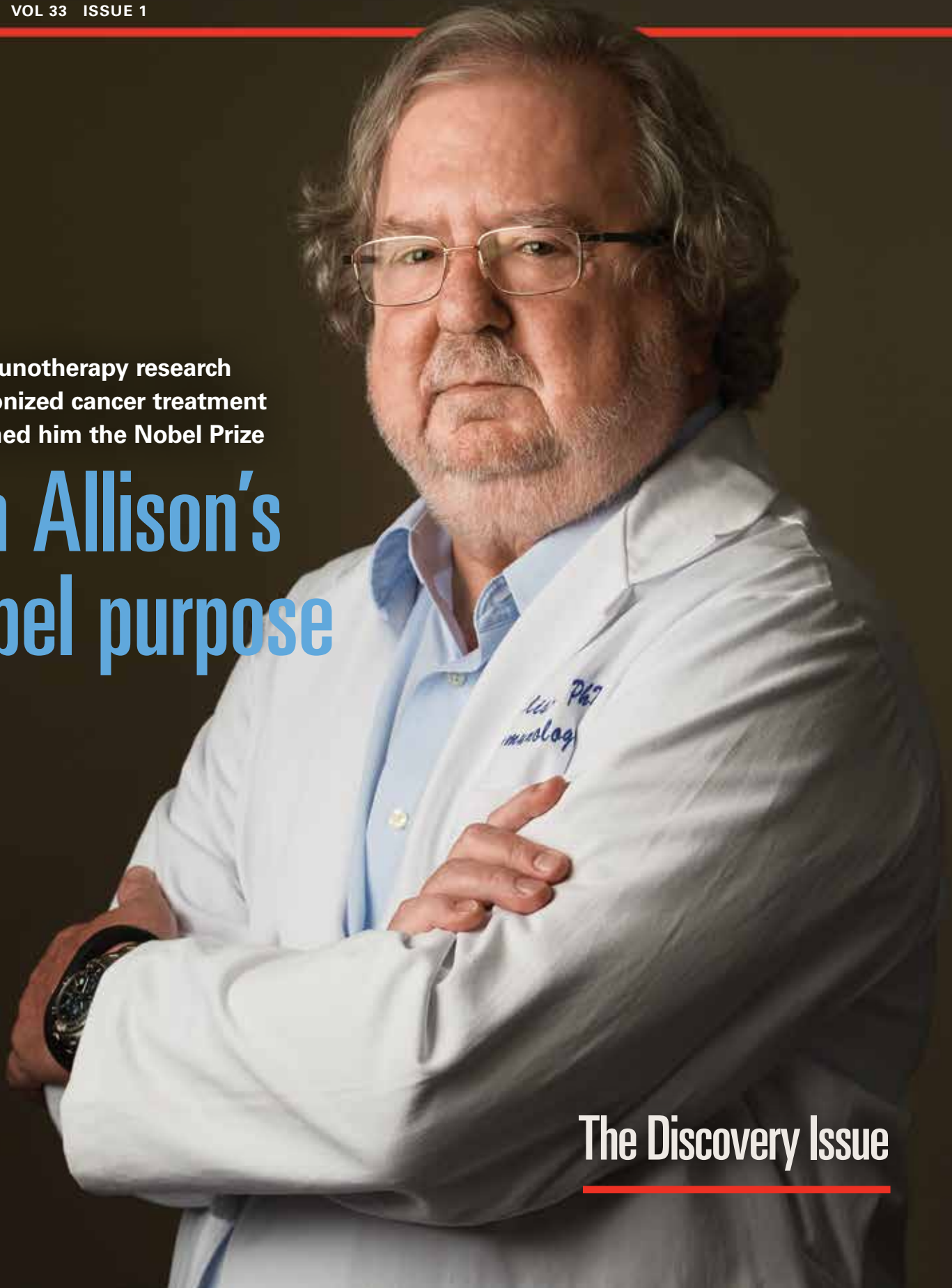
THE UNIVERSITY OF TEXAS  
MDAnderson  
Cancer Center

Making Cancer History®

FALL 2018 VOL 33 ISSUE 1

His immunotherapy research  
revolutionized cancer treatment  
and earned him the Nobel Prize

## Jim Allison's Nobel purpose



The Discovery Issue

## 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.

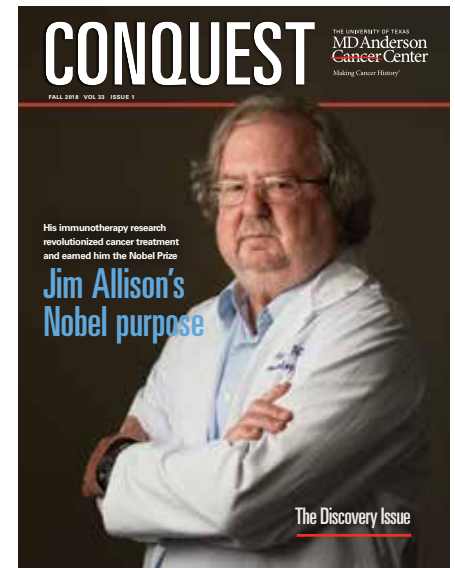
### Discovery

We embrace creativity and seek new knowledge.



A Comprehensive Cancer Center Designated by the National Cancer Institute

VISIT THE CONQUEST WEBSITE  
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## ON THE COVER

Jim Allison, Ph.D., is a blues-loving scientist from the small town of Alice, Texas, who shook off immunotherapy naysayers and made believers out of everyone when he figured out how to turn the immune system against tumors.

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FALL 2018

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# The Discovery Issue

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**F**or more than 75 years, MD Anderson has attracted many of the brightest minds in research and medicine to Houston, where they've changed the world and the way cancer is treated through innovation, creativity and breakthroughs.

Their commitment has resulted in improved outcomes and a steady rise in survival rates for cancer patients around the world. This tradition of discovery continues today, as further advances lay the foundation for even better cancer care tomorrow.

MD Anderson research focuses on four key areas: basic, translational and clinical research, and prevention and personalized risk assessment. Here's what that means ...

**Basic science research** — Seeking solutions to the critical problems that apply to fundamental aspects of genetics, molecular biology, cell and developmental biology, and tissue regulation. MD Anderson has seven centers targeting the basic science areas most likely to advance knowledge about cancer.

**Clinical research** — Improving patient care through the study of new drugs and other therapies in clinical trials. This research is pushing the envelope of early detection and treatment, personalized care and immunotherapy.

**Translational research** — Facilitating the movement of new ideas and treatments from the laboratory to the clinic, as well as the movement of clinical observations from the clinic to the laboratory.

**Prevention research** — Investigating ways to reduce an individual's risk of getting cancer. Discoveries are translated into advances in clinical care and recommendations to the community as a whole.

This issue of Conquest highlights only a few of the many scientific pursuits that have led to major breakthroughs in treating and understanding cancer, as well as current efforts underway. While we're unable to fit every deserving discovery in the pages that follow, we hope to inspire a craving for curiosity with these.

**Ipilimumab (green)** — the first immune checkpoint blockade drug approved by the Food and Drug Administration for metastatic melanoma — is shown bound to **CTLA-4 (cyan)**, a protein on T cells that shuts down immune response. The drug resulted from the work of MD Anderson chair of Immunology Jim Allison, Ph.D., who invented immune checkpoint blockade as a cancer therapy. His pioneering research, which led to the development of an antibody to block CTLA-4 and free the immune system to attack cancer, earned him the Nobel Prize.







Photo: Nick de la Torre

Phil Jones, Ph.D., leads MD Anderson's Therapeutics Discovery division, whose drug development experts benefit from their close proximity to patients and leading oncologists.

# Drawn to discovery. Driven by a purpose.

Four scientists explain what attracted them to Therapeutics Discovery's unique model for drug development

By Clayton R. Boldt, Ph.D.

“From the bench to the bedside” is a phrase often used to describe a drug discovery's journey from the laboratory to the clinic, where patients benefit.

MD Anderson's Therapeutics Discovery division, however, takes a different approach by beginning with the bench at the bedside. This drug discovery engine conducts research informed by the clinic, from start to finish.

“We are completely driven by unmet needs we see in the patients who come to MD Anderson for help,” says Phil Jones, Ph.D., vice president of Therapeutics Discovery. “Guided by the expertise of our world-class clinicians, our efforts begin with the patient and their cancer. The Therapeutics Discovery model is designed to develop new treatments to meet their needs.”

Composed of three Moon Shots Program™ platforms and the Neurodegeneration Consortium, Therapeutics Discovery is working hard to bring transformational, lifesaving medicines to patients quickly, safely and effectively. These medicines range from new chemical compounds to antibodies and cell-based therapies.

Unlike typical pharmaceutical companies, Therapeutics Discovery was built within the walls of MD Anderson, placing drug development expertise in unparalleled proximity to patients and leading oncologists. It's a recipe for success that is yielding promising results.

And at the heart of it all are more than 100 scientists, driven by a passion to see their work one day save a patient's life.



## The Institute for Applied Cancer Science (IACS) ▶

IACS is devoted to inventing new small-molecule drugs, or chemical compounds, that target specific vulnerabilities in cancer cells.

Principal research scientist Mick Soth, Ph.D., is a lead chemist for one of IACS' drug discovery projects, and is responsible for designing the safest and most effective compounds possible.

Soth spent more than a decade working for a major pharmaceutical company, but grew increasingly frustrated by limited successes and a lack of meaningful collaborations. He chose to join MD Anderson five years ago to find a new, more productive environment for drug development.

"I'm very excited about building something here," Soth says. "We're in a great spot to do drug discovery, with direct connections to MD Anderson clinicians, and we're building up what could become an operation that will elevate the institution, Houston and the state of Texas. That's really cool."

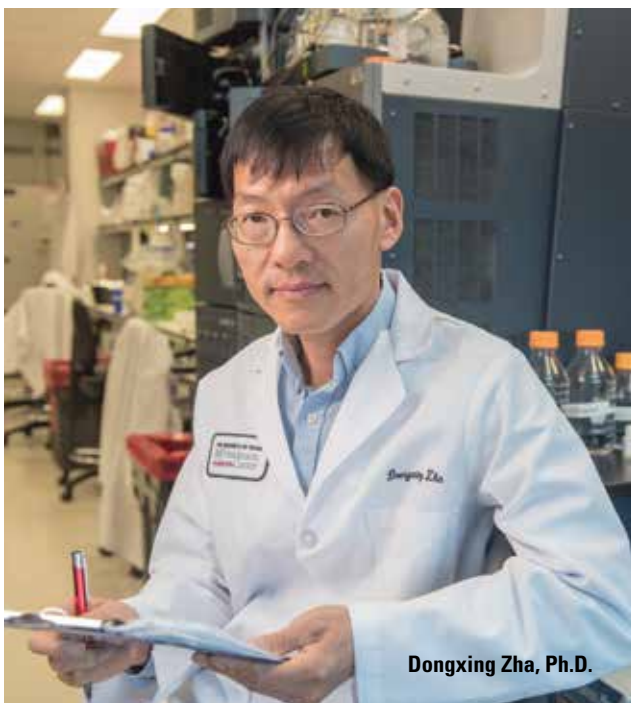
Soth already has two projects advancing to clinical trials early next year. That type of rapid success, coupled with collaboration, was exactly what he was looking for.

But what ultimately makes it all worthwhile?

"The first patient who is actually helped," Soth says.



Mick Soth, Ph.D.



Dongxing Zha, Ph.D.

## ◀ Oncology Research for Biologics and Immunotherapy Translation (ORBIT)

The ORBIT platform develops antibodies that recognize specific targets to either seek and destroy cancer cells or stimulate the immune system to attack a tumor.

Dongxing Zha, Ph.D., associate director of ORBIT, brought decades of research and antibody development experience with him when he joined MD Anderson four years ago. He also brought personal experience, having lost his father to gastric cancer.

"Cancer is a horrible, horrible disease that affects almost everyone directly or indirectly," Zha says. "I really want to contribute and help find new drugs to help those patients who desperately need new therapies."

Zha was excited by the possibilities at MD Anderson, knowing he'd work closely with leading investigators and draw from their deep understanding of cancer biology. With his team's expertise in drug development, he felt it was a win-win opportunity.

In a few short years, his team has developed two drugs, one now in clinical trials and another soon to be.

"I'm very excited and extremely proud of our work, and it's only possible at MD Anderson," says Zha. "We couldn't deliver this anywhere else."

## Therapeutics Discovery's recent accomplishments

### IACS/CCCT

Researchers in IACS and CCCT have discovered a drug that blocks a vital metabolic process required for cancer's growth and survival. The drug, IACS-10759, is now in clinical trials for acute myeloid leukemia (AML) and solid tumors.

### IACS/NDC

In 2018, MD Anderson and Accelerator Life Science Partners launched Magnolia Neurosciences, a company developing neuroprotective medicines based on discoveries made by IACS and the NDC.

### ORBIT

Researchers with the ORBIT platform developed a novel antibody, h8F4, that targets and selectively kills AML cancer cells. With the support of Astellas Pharma Inc., the new therapeutic will soon enter clinical trials.



Angela Harris

### ◀ Center for Co-Clinical Trials (CCCT)

Therapeutics Discovery's CCCT works at the crossroads of pre-clinical testing and validation of new drugs, which leads to a better understanding of how the drugs that are developed work and who will benefit most from them.

Angela Harris, an associate scientist on the in vivo pharmacology team, was born and raised in Houston. For her, working at MD Anderson was a "dream job." She spent 12 years with a Houston-area pharmaceutical group, but jumped at the chance to bring her expertise to MD Anderson four years ago.

"It's a great privilege to interact and collaborate with all the amazing scientists, project leaders and clinicians here," she says. "It's all teamwork, and that collaborative environment is so important to success."

Harris conducts preclinical experiments with new therapeutics to learn how safe and effective they might be for treating cancer in humans. The results of her team's work form the basis for decisions on whether or not to move into clinical trials and which patients should be treated with the new therapies.

"That's what we're all here for," she says. "I think we'll make a difference in patients' lives. That's what motivates me to be here. If what we're working on is able to help patients, that would be tremendously fulfilling."

### Neurodegeneration Consortium (NDC) ▶

The NDC is a multi-institutional initiative established in 2012 by an inaugural gift of \$25 million from the Robert A. and Renee Belfer Family Foundation to better understand neurodegenerative diseases and to develop new therapies to treat them. The NDC includes researchers from Therapeutics Discovery, Baylor College of Medicine, the Massachusetts Institute of Technology and the Icahn School of Medicine at Mount Sinai in New York.

Paul Acton came to the NDC with a personal and professional passion to take on Alzheimer's disease. Having watched four people in his family diagnosed with or succumb to the disease, he chose to devote himself to developing new treatments more than 25 years ago.

"It's definitely something that is real for me and gets me out of bed in the morning," Acton says.

He has worked for a number of major pharmaceutical companies over the years, but he never thought he'd work at a cancer center. However, he was impressed by the talent of the colleagues in Therapeutics Discovery and the infrastructure available at MD Anderson.

As a senior research scientist, Acton leads drug discovery efforts for the NDC. While the focus of the NDC's work is Alzheimer's disease, the drugs developed there may also benefit cancer patients suffering from the neurodegenerative and neurocognitive side effects of chemotherapy.

Losing several family members to cancer has allowed Acton to witness these side effects. Driven by this experience, he has made it one of his goals to help these patients.

"My hope is to get a drug not just into the clinic, but through the clinic and to the patients to make a difference in their lives."



Paul Acton

Photos by Wyatt McSpadden



# From South Texas to Stockholm



In addition to proving CTLA-4 acts as a brake on the immune response, Allison helped show that CD28 sparks an immune response — much like a gas pedal — when activated.

## Pioneering cancer researcher Jim Allison’s path to the Nobel Prize

By Scott Merville

It’s been almost 30 years since the Nobel Prize in Physiology or Medicine was given for a cancer therapy. That changed on Oct. 1 when Jim Allison, Ph.D., received the 2018 award for launching an effective way to free the immune system to attack cancer. He’s the first MD Anderson scientist to win the world’s most prestigious honor.

It was around 4:30 a.m. in Houston when Thomas Perlmann, secretary of the Nobel Committee for Physiology or Medicine, made the announcement in Stockholm:

“The Nobel Assembly at Karolinska Institute has today decided to award the 2018 Nobel Prize in Physiology or Medicine jointly to James P. Allison and Tasuku Honjo for their discovery of cancer therapy by inhibition of negative immune regulation.”

Allison, chair of Immunology and executive director of the immunotherapy platform for the Moon Shots Program™, pioneered a revolutionary cancer treatment that frees

the immune system to attack tumors.

“By stimulating the ability of our immune system to attack tumor cells, this year’s Nobel Prize laureates have established an entirely new principle for cancer therapy,” Perlmann noted in announcing the award to Allison, who shares the prize with Japan’s Tasuku Honjo, M.D., Ph.D.

### Taking the brake off T cells

The Nobel Prize recognizes Allison’s breakthrough work with T cells, the “soldiers” of the immune system that battle invaders and abnormal cells like cancer, bacteria and viruses. While T cells are fierce opponents of disease, they don’t attack every invader that comes along. If they did, the body would be in a constant state of fever, rash, inflammation or other immune system response. “Brakes” on the immune system prevent T cells from attacking everything, which is, in part, how cancer is able to develop.

Allison showed that the protein CTLA-4,

which is found on the surface of T cells, acts as a brake — a type of immune system checkpoint the body uses to avoid a dangerously over-reactive immune response. He then developed an antibody to block CTLA-4’s “braking” action, freeing T cells to attack cancer.

His work and determination led to the development of ipilimumab, the first in a class of drugs known as checkpoint inhibitors. In 2011, the drug — commercially named Yervoy — was approved for late-stage melanoma by the Food and Drug Administration. It has yielded unprecedented results. Twenty percent of patients with advanced melanoma who took the drug now live for at least three years, and many live 10 years and beyond. Subsequent research has focused on other immune system “brakes,” most prominently PD-1 and PD-L1, with drugs approved to treat certain types and stages of cancers such as melanoma, lung, kidney, bladder, gastric, liver, cervical, colorectal, head and neck and Hodgkin’s lymphoma.

Photo: David DuPuy



Photo: F. Carter Smith



**Top: Allison takes questions from reporters following a news conference in New York on Oct. 1, a few hours after learning he had won the Nobel Prize. Above: Allison received a rock-star reception from MD Anderson employees, patients, visitors and volunteers who gathered to celebrate and cheer the Nobel laureate.**

Clinical trials are underway in many other cancer types.

### The power of curiosity

“I never dreamed my research would take the direction it has,” says Allison, whose mother died of lymphoma when he was just 10. “It’s a great, emotional privilege to meet cancer patients who’ve been successfully treated with immune checkpoint blockade. They are living proof of the power of basic science, of following our urge to learn and to understand how things work.”

One of the most exciting aspects of immunotherapy, Allison says, is that it appears to continue working even after the treatment has stopped.

“The immune cells remain in the body. If the cancer comes back, the immune cells attack it.”

Allison says immunotherapy is quickly becoming the “fourth pillar” of cancer therapy, joining long-established treatments of surgery, radiation and chemotherapy.

“Immunotherapy won’t replace these other three, but it can be used in combination with them to offer patients the best chance to beat their disease.”

Allison will receive the Nobel Prize medal and diploma from King Carl XVI Gustaf of Sweden at the Nobel Prize award ceremony in Stockholm on Dec. 10. Since 1901, the Nobel Prize in Physiology or Medicine has been awarded 108 times to 214 Nobel laureates.

### Allison’s start in science

The son of a country doctor, Allison grew up in Alice, Texas, seemingly destined for medical school.

A lifelong interest in understanding how things work, and observing his father practicing medicine day-in and day-out, led to a decisive conclusion.

“I had a pretty good look at what it’s like to be a physician. As a doctor, you can’t make mistakes, you have to always be right,” Allison says. “Scientists generate and test hypotheses, which are wrong most of the time, otherwise you’re not asking the hard questions. Scientists only need to be right some of the time — preferably about important things.”

He shifted out of pre-med studies at The University of Texas at Austin, took a degree in microbiology and then went on to earn his doctorate in biological sciences in 1973.

Since then, Allison has been right often enough about important things to have a major impact in medical care — an impact that has saved the lives of countless cancer patients.

“Jim Allison’s research has led to life-saving treatments for people who otherwise would have little hope,” says Peter WT Pisters, M.D., president of MD Anderson. “The significance of immunotherapy as a form of cancer treatment will be felt for generations to come.”

### First stop: Smithville

Allison started his career at MD Anderson in 1977, arriving as one of the first employees of the institution’s Science Park, a new basic science research center located in Smithville, Texas, where he made his first major discoveries. He was recruited back to MD Anderson in 2012 to lead the Immunology Department and to establish an immunotherapy research platform for MD Anderson’s Moon Shots Program™.

In between came prominent positions as the leader of the immunology programs at the University of California, Berkeley, and Memorial Sloan-Kettering Cancer Center in New York.

“Science advances are the efforts of many,” Allison says. “A succession of graduate students, postdoctoral fellows and colleagues at MD Anderson, the University of California, Berkeley, and Memorial Sloan Kettering Cancer Center played important roles in this research.”

Allison’s ongoing leadership at MD Anderson focuses on improving knowledge of how these immune checkpoint inhibitors work in order to extend the benefits of immunotherapy to more patients with more types of cancer. His research continues, with his attention aimed at





**An enthusiastic crowd greeted Allison and a drumline-led procession as they made their way across the skybridge to Pickens Tower.**

the details of immune response to cancer and identifying new targets for potential treatment.

**There's still work to be done**

Under his leadership, with Scientific Director Padmanee Sharma, M.D., Ph.D., the immunotherapy platform conducts immune monitoring by analyzing tumor samples before, during and after treatment, in order to understand why these drugs work for some patients but not all. The platform works with more than 100 immunotherapy clinical trials at MD Anderson that are addressing a variety of cancers. The platform also collaborates with pharmaceutical companies to help them develop new drugs and combinations to better treat cancer.

“We need these drugs to work for more people,” Allison says. “One challenge is that the clinical success has outrun our scientific knowledge of how these drugs work and how they might best be combined with other therapies to improve treatment and reduce unwanted side effects. We need more basic science research to do that.”

Allison has collaboratively worked with scientists around the globe to expand the field of immunotherapy. He is a co-leader of the Stand Up To Cancer-Cancer Research Institute Cancer Immunology Dream Team and MD Anderson's director of the Parker Institute for Cancer Immunotherapy (PICI). Allison also is deputy director of the David H Koch Center for Applied Research of Genitourinary Cancers at MD Anderson and holds the Vivian L. Smith Distinguished Chair in Immunology.

Crucial funding for his research over the years has come from the National Institutes of Health, particularly the National Cancer Institute, the Cancer Prevention & Research Institute of Texas, Howard Hughes Medical Institute, the Cancer Research Institute, Prostate Cancer Foundation, Stand Up To Cancer and PICI.

# Allison's award-winning accomplishments

- Born Aug. 7 in Alice, Texas **1948**
- Takes his first faculty position at MD Anderson's Science Park in Smithville, Texas, where he develops a research interest in T cells **1973**
- At Berkeley, Allison publishes a paper in Nature that proves CD28, a molecule on the surface of T cells, acts as the gas pedal for the immune system. **1977**
- Reports in a Science paper that blocking CTLA-4 with an antibody unleashes an immune response against cancer in experimental models, curing 90 percent of cases **1982**
- The Food and Drug Administration approves the anti-CTLA-4 antibody ipilimumab, now known as Yervoy, for treatment of late-stage melanoma after the drug becomes the first to extend the survival of these patients. **1992**
- Wins first AACR-CRI Lloyd J. Old-CRI Award in Cancer Immunology given by the American Association of Cancer Research **1995**
- The journal Science names cancer immunotherapy its 2013 Breakthrough of the Year. **1996**
- Wins the Lasker-DeBakey Clinical Medical Research Award, the nation's highest honor for clinical research **2004**
- Is included on Time magazine's list of "The 100 Most Influential People" **2011**
- Wins the inaugural Sjoberg Prize from the Sjoberg Foundation and the Royal Swedish Academy of Sciences **2012**
- Earns his doctorate in biological sciences from The University of Texas at Austin **1973**

In his first major finding, at Smithville, Allison identifies the protein structure of the T cell receptor, the ignition switch for immune response, with papers in the Journal of Immunology and Cell. **1977**

In a paper in the Journal of Experimental Medicine, Allison shows that the protein CTLA-4 acts as a brake on T cells, halting immune response. **1982**

Becomes chair of the Immunology program at Memorial Sloan-Kettering Cancer Center in New York **1992**

Allison returns to MD Anderson to lead the Immunology department and the new immunotherapy platform for the Moon Shots Program. The institution invests \$40 million in the platform, including a \$10 million grant from the Cancer Prevention and Research Institute of Texas. **1995**

Allison, along with Tasuku Honjo, M.D., Ph.D., of Kyoto University's Faculty of Medicine in Japan, wins the Tang Prize for Biopharmaceutical Science. **1996**

Becomes MD Anderson director of the Parker Institute for Cancer Immunotherapy, a new \$250 million effort by social media billionaire Sean Parker to advance the field **2004**

Awarded the King Faisal Prize for Medicine from the King Faisal Foundation, Dr. Paul Janssen Award for Biomedical Research from Johnson & Johnson, the Albany Medical Center Prize in Medicine and Biomedical Research, and the Nobel Prize in Physiology or Medicine **2011**
- 2013**
- 2014**
- 2015**
- 2016**
- 2017**
- 2018**



**“I remember hearing her heels as she came down the hall to the clinic room. She had tears in her eyes and said ‘Colleen, there’s nothing, absolutely nothing there. The cancer is gone.’”**

*— Colleen Wittoesch, stage IV melanoma survivor*

The tumors that spread to Colleen Wittoesch’s brain disappeared after she participated in a clinical trial of two immunotherapy drugs.

## **T cells** jump the blood-brain barrier to **attack metastatic tumors**

A breakthrough clinical trial uses immunotherapy combination to target melanoma that has spread to the brain

By Scott Merville

**C**olleen Wittoesch learned in March 2016 that she had late-stage melanoma in the most difficult way.

“I couldn’t get my thoughts together, I kept forgetting things,” she recalls. “One night I was talking to my daughter and she said ‘you don’t sound right, we need to take you to the ER.’”

An MRI scan showed 12 tumors in her

brain. A surgeon removed the two largest, which were applying pressure on her brain and affecting her thinking.

Wittoesch then sought treatment at MD Anderson, where she had volunteered for 12 years, seven of those in the Melanoma Clinic.

For stage IV melanoma that has spread to the brain, surgery and radiation can remove small tumors and provide relief from symp-

toms, but they don’t stop disease progression. Median survival for these patients is four to five months.

Melanoma brain metastases are known to be resistant to multiple types of chemotherapies. In addition, due to the poor prognosis associated with melanoma brain metastases, patients often are excluded by drug companies from clinical trials.



In 2016, this had started to change, and Wittoesch's oncologist, Rodabe Amaria, M.D., assistant professor of Melanoma Medical Oncology, enrolled her in a clinical trial of two immunotherapy drugs designed to free the immune system to attack cancer.

Not long after the three-month initial regimen of the drugs ipilimumab and nivolumab, Amaria had good news.

"I remember hearing her heels as she came down the hall to the clinic room," Wittoesch says. "She had tears in her eyes and said 'Colleen, there's nothing, absolutely nothing there. The cancer is gone.'"

That complete response has endured.

Results from Wittoesch's clinical trial were reported in August in the *New England Journal of Medicine*.

### Remarkable results with immunotherapy combo

"Historically, fewer than 20 percent of these patients survive for one year," says study leader Hussein Tawbi, M.D., Ph.D., associate professor of Melanoma Medical Oncology. With the immunotherapy combination in this study, 82 percent have survived to one year."

Of 94 patients in the single-arm study, at a median follow-up of 14 months, 24 (26 percent) had a complete response with no sign of disease, 28 (30 percent) had a partial response and two (2 percent) had stable disease. At nine months, 56 patients had no progression of their brain tumors.

Tawbi calls the absence of progression for that long with brain metastases "remarkable."

"This practice-changing study proved that you can start with immunotherapy first with these patients, tackling both brain tumors and disease elsewhere in the body at the same time," Tawbi explains. "And it opens up new opportunities for development of systemic therapies for metastatic melanoma."

All patients were treated with ipilimumab, which blocks the CTLA-4 checkpoint on T cells, in combination with nivolumab, which inhibits activation of the PD1 checkpoint. Normally, both checkpoints shut down T cells and block the anti-tumor immune response. Blocking the checkpoints allows T cells, white blood cells that serve as the targeted warriors of the immune system, to attack.

### Patients previously excluded from clinical trials

One reason patients with brain metastases had been excluded from clinical trials is that the blood-brain barrier — a tight vascular



Photo: Wyatt McSpadden

Rodabe Amaria, M.D., says immunotherapy is a promising treatment for many of her patients whose melanoma has spread to the brain.



Photo: Wyatt McSpadden

Hussein Tawbi, M.D., Ph.D., led the practice-changing study that empowered T cells to cross the blood-brain barrier.

construction of blood vessels serving the brain — prevents drugs from reaching tumors. Since immunotherapy empowers T cells to attack tumors, rather than treating tumors directly, the immune system cells can cross the barrier. There were, however, concerns about immune-related side effects.

"We were quite concerned going into the study about immunotherapy causing inflam-

mation and swelling in the brain, so this was closely monitored," Tawbi says. "In the end, only 5 percent of patients had swelling in the brain."

The most common brain-related side effect was headache, and most of these side effects were low grade and easily managed. Overall, 52 patients (55 percent) had more challenging side effects, with 19 patients (20 percent) having to leave the trial.

For Wittoesch, the main side effect of the treatment "was like having the flu. I was kind of shaky and sick at times."

### The trial is a lifesaver

"I've never had chemotherapy, but I have seen it up close, and it can be pretty harsh," she says, referring to her experience as an MD Anderson volunteer and with her father's cancer treatment years ago.

"Dealing with cancer can be such a difficult fight," she says. "Without this clinical trial, I wouldn't be here, and it's a great pleasure for me to know that this study will be used to help other people."

Tawbi notes that oncologists continue to work with radiation oncologists and neurosurgeons to further improve outcomes and provide the best guidance for patients on initial treatment, as well as the best timing for subsequent treatments, if needed.

"Helping 57 or 58 percent of these patients is significant improvement, but our goal is to reach 100 percent," Tawbi says.

# Removing exclusions on immunotherapy

Patients with common autoimmune disorders such as arthritis aren't allowed to join clinical trials of the very effective treatment. Patrick Hwu, an expert in tumor immunology, is trying to change that.

By Michael Hardy

**P**eople used to ask Patrick Hwu, M.D., why he decided to devote his career to melanoma, a skin cancer with high mortality rates and limited treatment options.

"They would come up to me and say, 'How can you treat advanced melanoma? Isn't that depressing?' And actually, it was — my clinic of advanced melanoma patients used to turn over every six months. They used to all pass away, except for a very few."

That's starting to change, thanks largely to immunotherapy research by Hwu and others that explores treatments designed to boost a patient's immune system so it can better fight cancer. Since joining MD Anderson Cancer Center in 2004, Hwu's clinical and research work have investigated ways to improve outcomes for patients with melanoma, as well as other cancers resistant to more traditional therapies.

"Thanks to immunotherapy, we're having a lot of success now," says Hwu, who heads the division of Cancer Medicine. "Many of our patients are doing well for a number of years."

## A double-edged treatment

Immunotherapy supercharges the body's immune system, making it more effective at killing cancer cells. Unfortunately, it also makes the immune system more likely to attack healthy cells. Because of this, people with autoimmune disorders such as arthritis, psoriasis, colitis, lupus, celiac disease, multiple sclerosis and many other diseases that cause the body's immune system to attack itself were barred from the clinical trials of the first immunotherapy drugs.

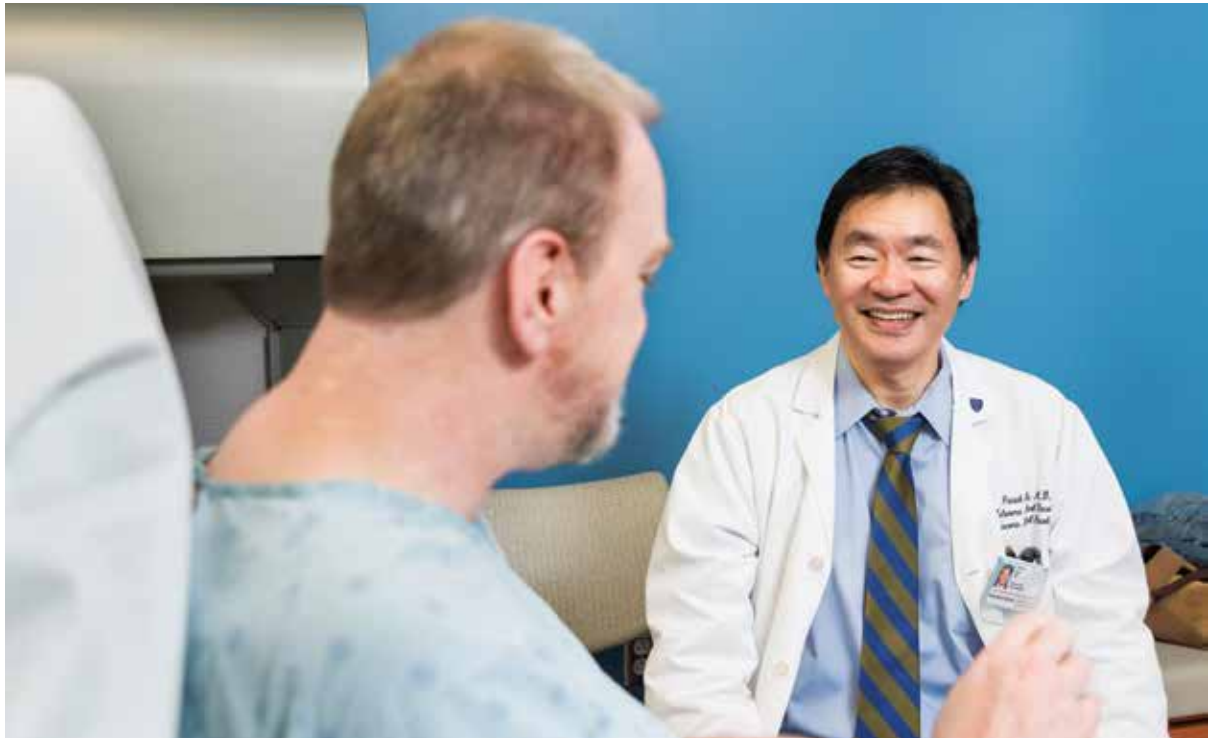
Autoimmune diseases are extremely common — an estimated one in every five people has one — which means a significant number of patients are excluded, for now, from some of the most promising new cancer treatments.

"We have patients who come to us who have both cancer and arthritis," Hwu says. "So, then what do we do?"

One such patient is Bob Wilkes, who already had arthritis and psoriasis before being diagnosed with stage 4







**Patrick Hwu, M.D., conducts leading-edge research exploring treatments designed to boost a patient's immune system so it can better fight cancer.**

melanoma. “When I learned I had cancer, my wife and I knew we faced an uphill battle, with surgery and chemotherapy in our future,” says Wilkes.

But when the couple inquired about immunotherapy, they learned Wilkes wasn't eligible because he had autoimmune issues.

“Immediately, my wife and I asked ‘Why not?’” Wilkes recalls. “Dr. Hwu's world-class research team responded to our question the same way and asked, ‘Why not indeed?’”

Wilkes, who owns a successful cabinet-building company headquartered in South Carolina, donated \$1 million to launch a research program that will help Hwu and his team contribute toward discovering new treatments for patients with cancer and autoimmune diseases.

“We want to find a way to cure not only cancer, but also autoimmune diseases,” Wilkes says. “We want to fight back.”

To extend the benefits of immunotherapy to people suffering from arthritis and other autoimmune disorders, Hwu and his research team, led by Roza Nurieva and Weiyi Peng, have been inducing arthritis and cancer in mice, then testing various treatments on them. The hope is to come up with a combination of drugs that will kill the cancer without exacerbating the arthritis. “You have these dueling effects,” Hwu explains. “You have one drug that stimulates the immune response to kill the cancer, and another drug that dampens the immune response to improve arthritis. Will they cancel each other out? Or can we distinguish the two pathways?”

### **A potential target**

The team's research has led them to focus on interleukin-17, or IL-17, a critical molecule that facilitates communication between immune cells. Many immunotherapy treatments

seek to boost production of IL-17 in order to better kill cancer cells. But according to Hwu's research, such treatments may do more harm than good, increasing autoimmunity without substantially improving the system's cancer-fighting abilities. If their hypothesis is borne out, cancer patients with autoimmune disorders could potentially take an IL-17 blocker to counteract the effects of their immunotherapy regimen.

Because immunotherapy is so powerful, even cancer patients without a diagnosed autoimmune disorder sometimes develop one during the course of treatment.

“We want to stimulate the cells that recognize the cancer without stimulating the cells that cause autoimmunity,” Hwu says. “We would be dead without our immune system, but our immune system can also wreak havoc.”

Hwu says that because immunotherapy treatments are so new — many have only recently gained approval from the Food and Drug Administration — researchers are still figuring out the best ways to use them.

“The immunotherapy revolution has just started in the past five years,” he says. “We've been working on it for decades, but the flurry of FDA approvals has just come in the past few years.”

One of the side effects of Hwu's research may be the development of better treatments for autoimmune diseases in patients without cancer.

Hwu compares the immune system to a squadron of tanks circulating in our bodies, guarding us from foreign invaders:

“You want the tanks around, but the problem is if these tanks accidentally have an issue and start firing away at other parts of your body. That's called autoimmunity. The goal of all these studies is to get the tanks to kill the cancer, but not kill our normal organs. Can we give a therapy that decreases the collateral damage? That's our whole goal as immunologists.”



# Where the BEST OUTCOMES begin

Melisa Bennett says she never had to worry that there might be a better option than MD Anderson for her cancer treatment.

From diagnosis to treatment and beyond, MD Anderson experts help breast cancer patients get back to living normal lives

By Claudia Feldman • Photos by Wyatt McSpadden

**M**elisa Bennett had regular well-woman exams. She had annual mammograms. And when she discovered what seemed to be a common skin condition on her right breast, she went to two different dermatologists.

If she had known then what she knows now, Bennett would have gone straight to MD Anderson Cancer Center. Instead, two years went by before the second dermatologist performed a biopsy and found Bennett didn't have eczema, she had Paget disease of the breast, a rare type of cancer involving the skin of the nipple and, usually, the darker circle of skin around it.

"By then, my only option was a mastectomy," says Bennett, a physical therapist and mother of three.

Her cautionary tale reinforces an oft-repeated message from Kelly Hunt, M.D., professor and chair of MD Anderson's department of Breast Surgical Oncology: Where a cancer

patient goes first for treatment may be the most important decision she makes in controlling her health and saving her life.

"Three doctors knew about my problem (before it was diagnosed correctly)," says the 45-year-old Bennett. "I love those doctors. I've never felt angry with them. I just know that had I gone to MD Anderson from the beginning, the doctors there would have known what to do."

## A 'cocoon of care'

Hunt reinforces the message: MD Anderson is the right place for patients with cancers of all types — both common and rare. In the institution's Breast Surgical Oncology and Breast Medical Oncology departments alone, several hundred breast cancer experts devote their professional lives to eradicating the disease in its many forms. Paget disease of the breast is just one example. When Bennett visited Hunt in 2016, the



**“My doctors would stop and give me hugs, and the nurses and techs would, too. MD Anderson is this huge, giant place, but it’s really a small community.”**

*— Jana Pankratz,  
breast cancer survivor*



**A clinical trial allowed Jana Pankratz to begin her treatment for triple-negative breast cancer with a standard course of chemotherapy instead of surgery.**

surgeon ordered another mammogram and an ultrasound. When both tests were negative, Hunt knew to keep pressing. She ordered an MRI.

That’s when the disease, which had two years to spread, was clearly revealed.

“The staff gave me such confidence, 100 percent,” Bennett says, “and I never had to worry that there might be a better option somewhere else. The other patients and I walked around MD Anderson in a little cocoon of care.”

Breast cancer patients haven’t always felt the love. Fifty years ago, Hunt says, the standard treatments were so harsh

## **Breakthrough in breast cancer care**

In 1976, MD Anderson doctors demonstrated in clinical studies that “lumpectomy” followed by radiation therapy for breast cancer can be as effective as radical surgical mastectomy. The new procedure became a worldwide standard of practice and replaced the highly invasive and widely practiced radical mastectomy.



**Kelly Hunt, M.D., is a firm believer that where a patient chooses to begin treatment is the most important decision she will make.**

some described them as slash, burn and poison. Today, she says, doctors are able to treat patients with much more finesse.

### **Advances in breast cancer treatment**

Decades ago, all axillary lymph nodes would be removed during a mastectomy, then biopsied for evidence of disease. Now MD Anderson surgeons do sentinel node biopsies first, a process that shows which nodes are most likely to harbor cancer. By sparing the healthy tissue, patients experience fewer problems following surgery, including arm swelling, numbness, nerve damage and range-of-motion issues.

In the past, patients underwent surgery, then chemotherapy. Today, treatment often starts with chemo, which reduces the tumor size or eliminates it and, again, allows surgeons to save healthy tissue. Some patients are able to replace intravenous chemotherapy treatments with chemo pills, which are easier to take and sometimes reduce the extent of surgery needed.

Today, physicians know how their patients will tolerate radiation and recover from reconstruction, based on their genetic makeup.

“My colleagues in Radiation Oncology found a specific gene mutation that predicts which patients will have more fibrosis and scarring, which can result in a worse cosmetic result,” Hunt says. “We’re also understanding that immune therapies that have been very successful in lung cancer and melanoma might be effective in breast cancer, depending on the tumor’s genetics.”

### **Access to a robust clinical trials program**

Hunt points out that MD Anderson patients also benefit from access to clinical trials. They offer patients the first crack at promising new treatments, which means a win for them and a gift to future generations.

That was the hope of Jana Pankratz when she arrived in Hunt’s office in the summer of 2017 with a lump in her breast. Pankratz was expecting immediate surgery but jumped at the chance to participate in a clinical trial first.

“If I could help somebody in the future, that would be the best,” she says.

In August, Pankratz began a standard course of chemotherapy, which had a 50-50 chance of shrinking her aggressive, triple-negative tumor.

“Fortunately, mine was reactive — the tumor was shrinking so fast we were shocked,” she says.

But when her progress started to slow, the doctor in charge of the trial, Stacy Moulder, M.D., added another chemo drug to the mix. The combination worked.

“In my instance, the tumor completely shrank,” Pankratz says. “All you could see left was the marker clip.”

### **More specialists and fewer surgeries**

That’s when Pankratz returned to Hunt, who performed a lumpectomy on the right breast. During the same procedure, a plastic surgeon reduced the size of her left breast.

“At the end of the day, things were a little more symmetrical,” Pankratz says.

During the lumpectomy, pathologists were able to check breast tissue samples to make sure all evidence of disease was gone.

“They said, ‘take out a little bit more just to be sure,’” says Pankratz, 57.

This attention to detail prevented the need for another surgery, she says. In some hospitals, she adds, patients have to wait days for those test results, then undergo additional surgeries. Most likely, the breast reduction would have been a third surgery.

Pankratz still required one final step — 30 days of radiation. She considered staying in Austin, where she lives, to have the daily treatments, but she felt so comfortable at MD Anderson that she rented a small apartment near the Texas Medical Center for the month.

“That time will always be near and dear to my heart,” says Pankratz, who is married and has one adult son. “I’d walk the hospital’s skybridge for exercise, and the people who drive the carts (carrying patients and others between Mays Clinic and the Main Building) would say, ‘Hey, how are you?’ My doctors would stop and give me hugs, and the nurses and techs would, too. MD Anderson is this huge, giant place, but it’s really a small community.”

### **Remaining on high alert**

She finished her treatments this past May, but needs to be vigilant for the next five years.

“Sure, I worry,” says Pankratz, who worked in administration for The University of Texas System for more than two decades. “It was a driving force in my decision to retire.”

Pankratz says she didn’t want to spend the next five years sitting behind a desk planning someone else’s time.

“I used to do everything at the speed of light, but this has been a message to slow the heck down. I’m a much calmer and more centered person after all this, I really am.”



Photo: Wyatt McSpadden



**Melody Laughbaum's surgeon used tissue from her abdomen to reconstruct her breasts.**

# RECONSTRUCTING HOPE

## Breast cancer survivors have many options

By Ronda Wendler

**W**hen cancer invaded Melody Laughbaum's left breast, she went into survival mode. The busy mother of four opted for a double mastectomy, even though her right breast was fine.

"That was my choice," she says. "I worried cancer would migrate to my healthy breast. So, I told my doctor, 'Get rid of them both.'"

Laughbaum, 49, could have gone with a less extreme treatment. She could have had chemotherapy and radiation, and taken the drug tamoxifen to help slow or stop cancer's spread. But this regimen would require frequent trips to the hospital, and she'd need to have a biopsy every six months to make sure the treatments were working and her cancer hadn't metastasized.

"Those repeated biopsies would carve away my breast tissue over time, like a mastectomy done in installments," she says. "Eventually I'd need plastic surgery to restore volume to my breast. And all the while, I'd worry the cancer might come back. I decided to have a double mastectomy and end this drama."

With her decision made, Laughbaum faced another dilemma: how to create new replacement breasts.

### Using what you've got

Breast reconstruction is performed in one of two ways: by replacing the missing breasts with silicone or saline implants, or by borrowing fat, muscle or skin from another area of the

body and sculpting it into a new breast — a technique known as autologous reconstruction.

Like Aretha Franklin's hit "(You Make Me Feel Like) A Natural Woman," Laughbaum wanted to avoid implants and "use what God gave me."

"I liked the idea of using my own flesh," she says. "There's something sensible about it. Once the scars and swelling went away, I'd still feel like me."

She chose a procedure where skin, fat and blood vessels are removed from the lower abdomen, transferred to the chest, and sculpted into a breast.

Taking tissue from the tummy is the most common way to do autologous reconstruction, says Alexander Mericli, M.D., assistant professor of Plastic Surgery.

"Tissue that normally would be discarded during a tummy tuck is instead fashioned into breasts," he says. "Patients love it. They get new breasts and a flatter tummy."

The inner thighs, back and buttocks can also supply tissue if a woman doesn't have enough abdominal fat.

Sculpting a breast from natural tissue tends to create a more natural look and feel than a breast implant, says Mericli, who performed Laughbaum's surgery. If a patient is having reconstruction on one side only, he notes, it's easier to match her healthy breast to one made of tissue than to one made from a silicone or saline implant.

Half of all breast implants need replacing

every 10 years, according to the American Cancer Society, but Mericli says autologous surgery typically is a one-time procedure.

"There's no implant," he explains, "so there's nothing to replace in the future."

The downside, according to the surgeon, is that tissue-transfer operations are complicated and can take as long as 12 hours to perform, whereas implants are done in only a few hours.

"Autologous surgeries also create more scars, because they require incisions in a second location on the body," Mericli says. "With implants, surgery is confined to the breast only."

### Still No. 1

The demand for autologous reconstruction is steadily rising, but implants remain the most popular way to build a new breast. Of the more than 106,000 women who had reconstruction last year in the United States, almost 87,000 opted for implants, according to the American Society of Plastic Surgeons. Just over 19,000 women chose autologous tissue transfer.

Implant surgery is usually a two-step process. First, a tissue expander, which is an empty breast implant, is inserted between the skin and chest muscle. Through a valve in the expander, the surgeon periodically injects saline to gradually fill the expander over several weeks or months.

After the skin over the breast area has stretched enough to accommodate a permanent implant, the expander is removed during a second operation and replaced with the silicone





Plastic surgeon Alexander Mericli, M.D., says breast reconstruction isn't an issue of vanity, it's a desire to "get back to where you were before cancer."

or saline implant. A sling or internal bra made of human or animal donor skin also is inserted to support the implant.

Some patients, particularly those with small breasts and pliable skin, may skip the expander step and receive implants immediately after mastectomy. And some patients are participating in an MD Anderson study that allows them to inflate their expanders at home with carbon dioxide gas.

"They appreciate not having to travel back and forth to the hospital," Mericli says.

### Reconstruction, tattoos and more

After the reconstructed breasts are in place, the plastic surgeon handcrafts new nipples during a separate and final surgery. Snipping, folding and stitching existing breast tissue into a peak, the surgeon creates a nipplesque protrusion for each breast. New nipples can also be crafted using pinkish tissue from the incision scar, the groin or between the buttocks.

Or, new nipples can be tattooed directly onto reconstructed breasts.

Angela Loveless is one of three MD Anderson nurses trained in this highly specialized technique.

"We use pigments in various hues to create a 3D 'picture' of a nipple that has no physical dimension, but it can look quite real," she says. "Shading makes the nipple appear to stick out. Our results are very realistic."

Because tattoos are permanent and rarely fade, one session is usually all that's necessary.

Tattoos also are used to add color to tissue-engineered nipples, if needed.

There is such a thing as a nipple- and skin-sparing mastectomy — Laughbaum had one — where the surgeon removes all the breast tissue while preserving the breast's skin, nipple, and areola — the dark ring of tissue around the nipple.

"It's like scooping the fleshy fruit out of an orange and leaving the skin intact," Mericli says.

The surgeon then places the implant or newly constructed breast mound inside this 'skin envelope.' However, in some patients the nipple and areola tissue can start to die because of insufficient blood supply.

To spare Laughbaum from this complication, Mericli salvaged her nipples and areolas, then stitched them above her hip bone. The "hipples," as Laughbaum and her medical team jokingly dubbed them, stayed there for six months, nourished by an ample blood supply while her newly reconstructed breasts healed.

"Looking in the mirror was weird, but kind of funny," says Laughbaum, who teaches elementary school art. "I felt like a Picasso painting."

### Many options, and they're all individualized

Reconstruction often can be performed at the same time as the mastectomy, which is called immediate reconstruction. Or it can be performed any time after the initial surgery — even years later. This is called delayed reconstruction.

Laughbaum had immediate reconstruction after her mastectomy.

"Breast tissue came out, then new breasts went in," she says, "all in one surgery."

For medical reasons, not all women are



**Jesse Selber, M.D., pioneered a minimally invasive, robotic surgery that helps breast reconstruction patients heal faster and more comfortably.**

## Robot surgery makes healing quicker and more comfortable

**W**hen a healthy woman with natural breasts has breast enlargement surgery, her existing breast tissue and muscle support her implants and keep them in place. But in a woman with cancer who's had a mastectomy, this breast tissue has been removed. And, if she's also undergone radiation treatment, the fatty and connective tissue that lies under the breast is further damaged by radiation and unable to support implants.

To anchor a mastectomy patient's implants, protect them from infection, and create a better cosmetic outcome, doctors cover the implants in one of two ways: with a manufactured material or with the latissimus dorsi muscle that is located in the mid and upper back.

Traditionally, the muscle is harvested by a surgical incision that leaves an 8-by-12-inch scar across the back. But Jesse Selber, M.D., professor of Plastic Surgery, has pioneered a minimally invasive, robotic surgery that helps patients heal faster and more comfortably.

Selber's technique uses the mastectomy incision along with three small incisions, each less than a half-inch in length, made under the patient's arm. Long, slender robotic arms are inserted through the tiny incisions and operated by a surgeon who sits at a console resembling an airplane cockpit. The robotic arms separate the muscle from the surrounding tissue, then tunnel it under the skin to the breast, where it's draped securely across the implant.

This procedure is routinely performed only at MD Anderson. The success rate, Selber says, is 100 percent.

"There's been no loss of muscle viability," he says, "and we've not had to convert to the more invasive technique."

good candidates for immediate reconstruction.

"Women with more advanced disease may need chemotherapy or radiation, which affect the body's ability to heal," Mericli says. "It's best for them to complete their cancer treatment, and then once they're determined to be doing well, undergo reconstruction at a later stage."

Not all women who undergo mastectomy have a cancer diagnosis.

"We see many women with high-risk profiles who choose to have a preventive mastectomy," Mericli says. "The vast majority undergo reconstruction. They're making an elective decision about removing their breasts, and are quite motivated to consider options to reconstruct their breasts at the same time."

It's not about vanity, he says, but it's about something much deeper.

"This is about getting back to where you were before cancer."

Mericli points out that the choices to be made in breast reconstruction, or whether to have it at all, are highly individualized.

"It's a very personal decision for each patient, and it's our responsibility as physicians to help guide them through the process, which can seem overwhelming."



**Emil J Freireich, M.D.**, professor of Leukemia, collaborated with the late Emil Frei, M.D., in the mid-1960s, to develop combination chemotherapy, which uses multiple drugs at once to fight cancer. This approach led to cures in more than 90 percent of children with acute lymphoblastic leukemia (ALL) — which almost always proved fatal prior to Freireich's research, and more effective treatments for various adult cancers including Hodgkin's lymphoma. Freireich and Frei's work in chemotherapy is believed to have saved the lives of more than 100,000 children. In addition, Freireich and colleagues designed continuous flow separators to divide whole blood from healthy donors into cellular components. The technique, first used to obtain white blood cells, was later adapted to collect lymphocytes for immunotherapy and stem cells for bone marrow transplantation.



Photo: Wyatt McSpadden

By Ron Gilmore

# History in the making

**MD Anderson's mission is to end cancer. Working each day alongside the many people providing nursing care, nutritious food, shuttle services, parking assistance, lab test analysis and other services are researchers and physician-scientists who have made history in understanding and treating cancer.**

**The cancer center is home to world-renowned experts who have ushered in medical "firsts," from life-changing drug discoveries to more efficient**

**methods for analyzing incomprehensible amounts of clinical study data.**

**These everyday heroes and heroines already have a place in the history books, but their contributions may not be apparent to patients who depend on their significant discoveries and achievements.**

**Here are five MD Anderson faculty members — just a few of the many — who moved cancer treatment forward through their trailblazing scientific work.**

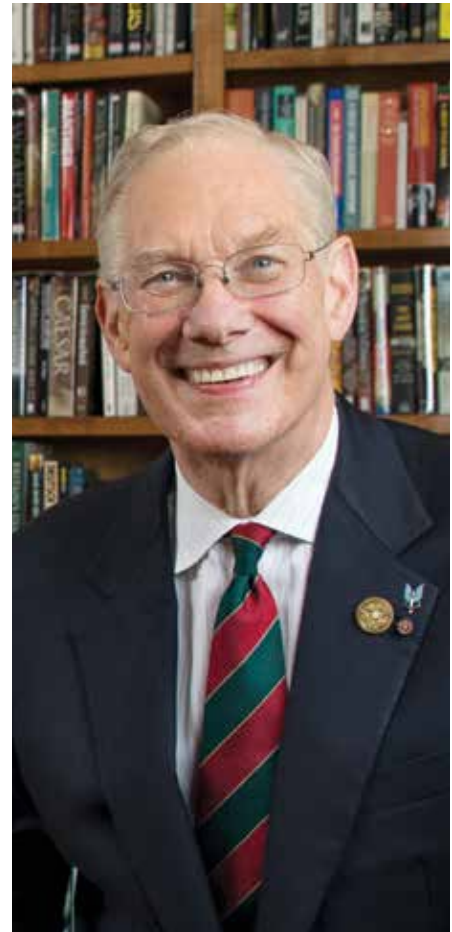
Photo: Adolfo Chavez III



**Gabriel Lopez-Berestein, M.D.**, professor of Experimental Therapeutics, in the 1980s developed an antifungal, liposomal-encapsulated agent for the treatment of potentially life-threatening systemic fungal infections that are common among patients with reduced immunity due to chemotherapy. Lopez-Berestein has been a prominent leader in experimental therapeutics and has conducted "bench-to bedside" translation of more than 20 compounds, with several FDA-approved drugs. His was the first lab to carry out pharmacokinetic and clinical trials of liposomal-based drugs in the U.S., and to develop several antifungal and antitumor therapeutics such as nystatin and anamycin. More recently, he pioneered the use of ncRNAs in Phase I trials.



**Maura Gillison, M.D., Ph.D.**, professor of Thoracic/Head and Neck Medical Oncology, played a key role, along with the late K. Kiang Ang, M.D., Ph.D., in recognizing that head and neck cancer patients who had tumors in the upper throat and tested positive for the human papillomavirus (HPV) had better overall survival than patients with HPV-negative disease. The study findings, published in 2010 in the *New England Journal of Medicine*, suggest that all patients with this common disease should be tested for HPV. Gillison and her team went on to show that HPV is responsible for several cancer types in men and women, including those in the back of the throat, in an area known as the oropharynx. About 70 percent of oropharyngeal cancers are linked to HPV, and the number of cases diagnosed is rising dramatically, according to the Centers for Disease Control and Prevention.



**V. Craig Jordan, Ph.D.**, professor of Breast Medical Oncology, is one of the world's pre-eminent experts in breast cancer research and treatment. Jordan is credited with reinventing the failed contraceptive drug tamoxifen as a breast cancer treatment. The drug, in existence since the 1960s, was originally created to prevent pregnancy by blocking estrogen. Jordan developed the strategy of long-term adjuvant tamoxifen therapy, and is often called the "Father of Tamoxifen." He also described and deciphered the properties of a new group of medicines called selective estrogen receptor modulators (SERMs). He first discovered the preventive abilities of tamoxifen and the drug raloxifene. In 1998, tamoxifen was approved by the Food and Drug Administration for reducing breast cancer risk in high-risk women. Tamoxifen remains one of the world's most successful cancer drugs and is on the World Health Organization's list of essential medicines. The drug is estimated to have saved the lives of millions of women around the world. The FDA granted approval for raloxifene in 2007. In addition to decreasing the risk of breast cancer in postmenopausal women who are at high risk for breast cancer, raloxifene also is prescribed to treat and prevent osteoporosis.



**Michael Andreeff, M.D., Ph.D.**, professor of Leukemia, is a pioneer in the development of flow cytometry, a method for counting and sorting cells that is commonly used in today's clinical trials. In 1971, Andreeff established the first flow cytometry laboratory at the University of Heidelberg and organized the first European meeting on the technique. This life-changing discovery allows scientists to quickly conduct cell counting, cell sorting,

biomarker detection and protein engineering by suspending cells in a stream of fluid that is passed through an electronic detection apparatus. Flow cytometry makes it possible to analyze the physical and chemical characteristics of thousands of particles per second. It's routinely used to diagnose health disorders, especially blood cancers, but has many applications in basic research, clinical practice and clinical trials.



# Tang Prize celebrates Mendelsohn's trailblazing work in targeted therapy

By Scott Merville

**T**argeted cancer therapy pioneer John Mendelsohn, M.D., researcher and former president of MD Anderson, was awarded a share of the 2018 Tang Prize in Biopharmaceutical Science for his leadership in developing antibodies to block cancer-promoting growth factor receptors on the surface of cancer cells.

Honored along with Mendelsohn were Tony Hunter, Ph.D., professor of Biology at the Salk Institute, and Brian Druker, M.D., director of the Oregon Health Sciences University Knight Cancer Institute.

In announcing the award on June 19 in Taiwan, the Tang Foundation noted the three awardees launched the field of targeted therapy — attacking tumors based on their genetic and molecular aberrations — with their research to understand the role of tyrosine kinase proteins and to design ways to block their activity.

Their work led to “a thorough understanding of the fundamental principles of cell growth and cancer development,” the Tang Foundation noted in its announcement, and the therapies they developed “fundamentally changed the practices of cancer clinics.”

Mendelsohn, who served as president of MD Anderson from 1996 to 2011, and was a professor of Genomic Medicine and director

**“Dr. Mendelsohn is an unparalleled servant leader. I am personally inspired and motivated daily by his example and his contributions to our mission to end cancer.”**

— *Peter WT Pisters, M.D.,  
president of MD Anderson*

of the Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy, announced his retirement in August. He was named President Emeritus following a unanimous vote by the UT System Board of Regents. Mendelsohn was also the L.E. & Virginia Simmons Senior Fellow in the Division of Health and Technology Policy at Rice University's Baker Institute.

The honor cites Mendelsohn's role in conceiving the approach of using antibodies to target the epidermal growth factor receptor (EGFR), which is overexpressed or mutated to a cancer-promoting form in a variety of cancers.

Then at the University of California at San Diego, working with colleague Gordon Sato, Ph.D., Mendelsohn's team conducted preclin-

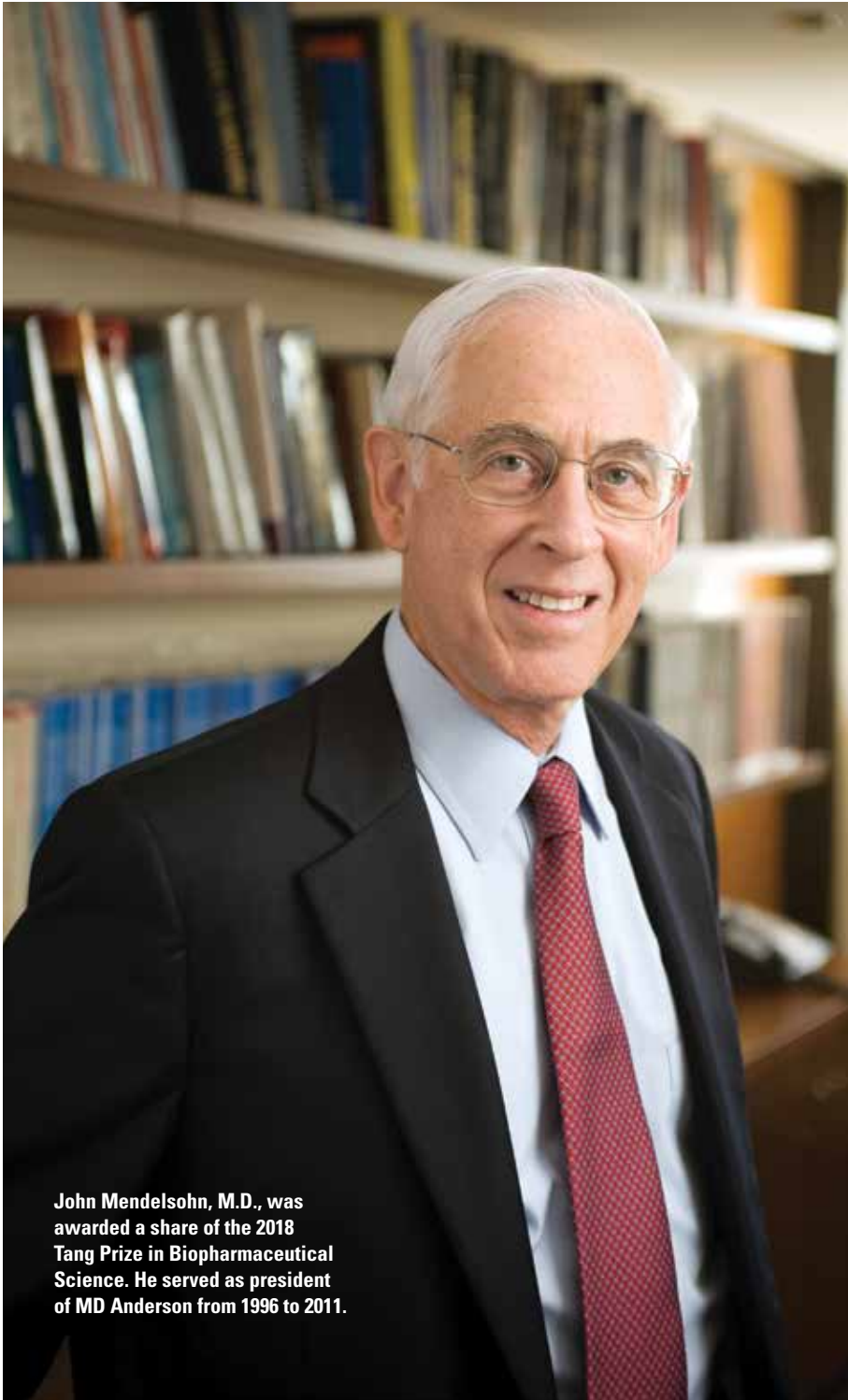
ical research and developed the anti-EGFR antibody cetuximab (Erbix), which went on to approval by the Food and Drug Administration for the treatment of colon cancer and head and neck cancer. This first tyrosine kinase-targeting antibody was “a trailblazer which has spurred many others to follow,” the Tang announcement noted.

Hunter discovered tyrosine phosphorylation and found that the Src oncogene is a tyrosine kinase. He also demonstrated the role of tyrosine phosphorylation in uncontrolled cancer growth.

Druker advocated for and led the successful clinical trial of imatinib (known commercially as Gleevec) for chronic myelogenous leukemia, the first successful small-molecule tyrosine kinase inhibitor.

“It's an honor to be recognized by the Tang Foundation with colleagues who opened such an important chapter of cancer research,” Mendelsohn says. “By highlighting the vital connection between basic research and progress in the clinic, the Tang Foundation encourages the progress we need in scientific, translational and clinical research to continue to improve cancer treatment.”

Established in 2012 by Taiwanese entrepreneur and philanthropist Samuel Yin, the



**John Mendelsohn, M.D., was awarded a share of the 2018 Tang Prize in Biopharmaceutical Science. He served as president of MD Anderson from 1996 to 2011.**

The South Campus Research Initiative enabled the development of the Red and Charline McCombs Institute for the Early Detection and Treatment of Cancer, as well as MD Anderson's largest fundraising campaign, Making Cancer History®: The Campaign to Transform Cancer Care. The effort generated more than \$1.2 billion in philanthropic commitments that have since fueled significant advances in patient care and research.

Under Mendelsohn's leadership, space for research expanded with construction of the George and Cynthia Mitchell Basic Sciences Research Building, home of the Institute for Basic Science.

He also guided the opening of the Lowry and Peggy Mays Clinic, the John Mendelsohn Faculty Center, the T. Boone Pickens Academic Tower, the Proton Therapy Center, a 320-bed addition above Alkek Hospital, and a 126-room expansion of the Rotary House International Hotel.

His innovative commitment to prevention research helped build what is now the Dan L. Duncan Building to house the Division of Cancer Prevention and Population Sciences, and established the Duncan Family Institute for Cancer Prevention and Risk Assessment to support research.

Tang Prizes are awarded every two years in four categories: Biopharmaceutical Science, Sustainable Development, Sinology (the study of Chinese language, history, customs and politics) and Rule of Law. Winners receive a medal and diploma and share a \$1.33 million cash award and a \$330,000 research grant.

During Mendelsohn's 15-year tenure as

president of MD Anderson, research expenditures jumped more than fourfold, from \$121 million in 1996 to \$547 million in 2010. MD Anderson became the nation's leading recipient of grants from the National Cancer Institute, greatly increased institutional research funding from clinical operations, and boosted external funding through philanthropy.





Lance Peytavin and his son, Christian, share a love of golf. They both also have a rare genetic disorder known as Li-Fraumeni Syndrome.

# Primed for cancer: Genetic disorder raises risk

By Katrina Burton

**C**hristian Peytavin is a typical teenager by all outward appearances. He plays video games and golf, and plans to become a computer programmer.

But two years ago, the high school junior was diagnosed with a rare hereditary condition that increases the risk of developing multiple cancers, often at an early age. The genetic disorder, known as Li-Fraumeni Syndrome, most often is associated with soft tissue and bone sarcomas, breast cancer, brain tumors, leukemia and adrenocortical carcinoma — a type of adrenal gland cancer.

About half of those with Li-Fraumeni will develop cancer by age 40, and up to 90 percent by age 60.

“It’s called the ticking time bomb disorder,”

says 17-year-old Christian. “People who have it may get several different cancers in their lifetime.”

Christian didn’t know he had the disorder until his father, Lance, was diagnosed with prostate cancer five years ago at age 41. His father’s cancer proved to be unusual.

“We thought we’d caught it early,” Christian recalls, “but it had already spread to his lymph nodes. Since then, he’s been through two surgeries, one clinical trial, immunotherapy and hormone therapy.”

When Lance’s cancer didn’t go away, he

underwent genetic testing in his Louisiana hometown. The results showed a mutation on his TP53 gene. The mutation causes the p53 protein, produced by the gene, to become damaged and unable to do its job of preventing cancerous tumors from developing.

Li-Fraumeni Syndrome was first recognized in 1969 by Drs. Frederick Li and Joseph Fraumeni Jr. while studying pediatric and familial cancers at the National Cancer Institute.

Subsequent research, initiated more than 30 years ago by MD Anderson genetics professor Louise Strong, M.D., helped confirm that TP53 — the most commonly mutated gene in people with cancer — is the underlying cause of Li-Fraumeni. This discovery led to the creation of MD Anderson’s LEAD (Li-Fraumeni



**Christian's sister, Kate, doesn't have Li-Fraumeni, but she worries about her brother and father's increased risk of cancer, says her mother, Anne.**

Syndrome Education and Early Detection) Program, which tracks Li-Fraumeni families and maintains the largest Li-Fraumeni database in the country.

"We started following patients and families that had several cases of cancer — too many to be a coincidence," Strong says. The family members we surveyed over the years lived in different locations and had different occupations, so we suspected their cancers had to be connected to a mutation in the genes."

Strong, whose career began in Pediatrics, says she was saddened to see kids survive one cancer only to develop another. Her research opened doors for more studies and discoveries.

Since then, Strong has helped develop a blood test that may indicate the presence of Li-Fraumeni. Several years ago, she teamed with Therese Bevers, M.D., medical director of MD Anderson's Lyda Hill Cancer Prevention Center, to offer whole-body MRIs that screen for genetic changes in adult patients.

At MD Anderson Children's Cancer Hospital, Najat Daw, M.D., professor of Pediatrics, heads the LEAD Pediatric Screening Program for patients ages 20 and under. Daw met the Peytavin family through the program when they came to MD Anderson for additional genetic testing.

"People with Li-Fraumeni have a 50 per-



Photo: Nick de la Torre

**In the 1980s, Louise Strong, M.D., helped confirm that the TP53 gene causes Li-Fraumeni. She also helped develop a blood test that may reveal the disorder.**

cent chance of passing the syndrome along to their children," Daw says. "It can be stressful for families to make the choice to proceed with genetic testing, but knowing your risk and your children's risk and taking preventive measures is important."

"I knew this could have a devastating effect on our two children," says Lance's wife,

Anne. "But we had to know, and we felt our kids needed to know what their risks were for developing cancer, so they could start early screening for their best chances at beating any cancers that may develop."

The family took their doctor's advice and underwent genetic testing. The results revealed Christian had Li-Fraumeni, but his sister, Kate, did not.

"I think the news hit Kate the hardest," says Anne. "Knowing that any day can be the day her brother and father are diagnosed with cancer is stressful for us all."

Christian will have frequent physical exams, blood tests and MRIs for the rest of his life to catch cancer early. Lance continues his prostate cancer treatment at MD Anderson where he is regularly screened for other possible cancers through the LEAD program. The family is staying positive and continuing to take one day at a time.

Kate, an aspiring actress and musician, has dedicated several YouTube songs to her father and brother. Christian is taking college-level courses in high school. When he graduates next year, he'll also be awarded a two-year college associate's degree.

"I've learned to just go for it, and keep pushing forward," he says. "I want to get the most I can out of life."



# For this operation, surgical instruments include **A GUITAR**

To preserve his talents, musician Robert Alvarez remained awake and performed during his brain tumor surgery

By Meagan Raeke

**T**he first few notes of Radiohead's "Creep" brought tears to the eyes of neurosurgeon Sujit Prabhu, M.D. "I thought, 'Oh my god — we pulled it off!'" recalls Prabhu, a professor of Neurosurgery.

The music wasn't coming from a speaker. It was coming from the other side of the sterile surgical drape, where 24-year-old musician Robert Alvarez lay on the operating table in MD Anderson's BrainSuite®, playing guitar during his brain tumor surgery.

While playing music during minimally invasive deep brain stimulations is relatively common, bringing a large instrument into an intraoperative MRI suite during open, awake brain tumor surgery is not, and the potential complications are much higher. But Prabhu and Alvarez agreed the challenge was worth it to protect what was most important to the young man: his ability to create music.

## **A patient-centric approach**

Alvarez was diagnosed with a low-grade brain tumor in 2013, when he was 19. Although the tumor crossed the insular, frontal and temporal lobes of his brain, he had few symptoms then. He was worried about the risks of surgery and decided to postpone treatment to focus on his music career. The choice made a distinct impression on Prabhu when they met in January 2018, after Alvarez began having seizures.

"How many people will sit with a brain tumor for years and

be creative, knowing you have a ticking time bomb?" Prabhu asks. "At any cost, he wanted to play music."

To take out the tumor, Prabhu would have to navigate through areas of the brain connected to speech, motor function, emotions, memory and mood.

"A complication in these areas as a result of surgery would take away his ability to play," Prabhu says. "We're still at a crossroads trying to understand brain connectivity as it relates to individual patients. We know certain areas of the brain control certain functions, but the connections are much more complex than we ever thought."

## **An awake craniotomy**

Neurosurgeons use sophisticated tools before and during surgery to map these connections in order to protect critical brain functions. When the tumor is in an area of the brain that controls speech, motor or sensory function, the best approach is a surgical procedure called an awake craniotomy.

During the surgery, the patient is awakened mid-surgery for a series of simple neurological tests. This gives the neurosurgeon valuable, immediate feedback about how much tumor can be safely removed. Doctors at MD Anderson perform nearly 100 awake craniotomies every year.

"We have to be very precise," Prabhu says. "Even a few millimeters can make a difference."

The brain has no pain fibers, so applying local anesthetic



Robert Alvarez played a guitar while undergoing brain cancer surgery, which helped doctors protect critical areas of his brain that control motor function, speech, memory and mood.





**When Alvarez's playing faltered during surgery, the health care team backed off and operated on a different part of the tumor.**

to the surrounding skin, muscle and dura mater allows the patient to remain comfortably awake for the critical part of the surgery. Prabhu recognized that the ability to create music, however, is far more complex than the standard neurological tests could convey.

"Music comes from the heart," Prabhu says.

### **Maintaining patient safety**

To protect the young musician's livelihood, Prabhu asked Alvarez to play the guitar during surgery. That presented several challenges:

- The surgery took place in the BrainSuite, a specialized neurological operating room with an MRI magnet weighing 7.5 tons. The magnet would easily pull in Alvarez's electric guitar, so he bought and practiced with an acoustic guitar for the surgery.
- Usually, patients lay on their side for an awake craniotomy. Most musicians play the guitar sitting or standing. The team had to find a compromise that would allow Alvarez to play comfortably with his head fixed in place while Prabhu operated.
- A sterile surgical field is necessary to prevent infection, but Alvarez couldn't play the guitar if he was literally draped in surgical drapes. The OR nursing team suggested using MRI-safe poles to hang the surgical drapes like curtains instead. "Our primary focus is making sure the patient is safe," clinical OR nurse Michelle Brents says. "We keep the same safety standards because when you change things, you can end up with problems."

To avoid problems, the entire team planned extensively. Brents joined Alvarez, Prabhu, neuroanesthesiologist Shreyas Bhavsar, D.O., two MRI technologists and a surgical technician in the BrainSuite for a dry run the day before surgery.

"We brought him in a day early to get him familiar with the environment and to make sure the draping and positioning



**Neurosurgeon Sujit Prabhu, M.D., says everything "worked like a symphony" during his patient's awake craniotomy.**

we planned would be feasible," Bhavsar explains.

The next day, "everything just worked like a symphony," Prabhu says.

Alvarez sang the same tune and played the same rhythm he had the day before. At times, when his playing faltered, Prabhu backed off and operated in a different part of the tumor.

"I removed more of the tumor than I expected," Prabhu says. "I wouldn't have pushed it as much if he wasn't playing the guitar."

Prabhu safely removed 90 percent of the grade II astrocytoma brain tumor. After healing from surgery, Alvarez completed proton therapy and began chemotherapy this past summer.

"I'm looking forward to chemo being finished, but I'm still playing my guitars and writing lyrics," Alvarez says. "I'm just really grateful."



**Najat Daw, M.D., leads a study examining the delivery of chemotherapy through an inhaler — the same type used in asthma treatment.**

# STRAIGHT TO THE LUNGS

Inhaled chemo lessens collateral damage

By Katrina Burton

**A** new way of treating cancer that spreads to the lungs from another site in the body is being studied at MD Anderson Children’s Cancer Hospital.

“Certain cancers that spread to the lungs are treatable with intravenously delivered chemotherapy drugs,” says Najat Daw, M.D., professor of Pediatrics and lead investigator of the study. “However, this traditional method of delivering chemo into the bloodstream can cause the drugs to reach organs such as the liver, kidneys, brain and bone marrow, with less chemo getting to the lungs. This can cause organ damage and in rare cases, death.”

Daw and her colleagues are studying the feasibility and safety of delivering the anti-cancer drug gemcitabine through an inhaler — the same type used in asthma treatment. Patients ages 12 to 50 years old who have lung tumors that developed from cancer that originated elsewhere are eligible to participate.

Inhalation chemotherapy, as it is called, was first tested and proven effective in mice in a laboratory study led by Nancy Gordon, M.D.,

assistant professor of Pediatrics, and Eugenie Kleinerman, M.D., professor of Pediatrics at MD Anderson. Further studies showed the therapy also helped lessen metastasized lung tumors in dogs with osteosarcoma, the most common type of pediatric bone cancer.

The current study targets lung tumors that have developed from all types of solid tumors in children and adults, not just osteosarcoma. Participants are first required to take a pulmonary function test.

“Pulmonary testing is extremely important before any treatment is administered,” says Gordon, the trial’s co-principal investigator. “It lets us know if the patient is well enough to handle the treatment.”

Each treatment lasts 15 to 30 minutes and is given in the hospital twice a week. Treatment duration can last from one month to one year, depending on the patient’s tolerance and tumor response.

Blood samples are collected to measure the amount of drug that may enter into the bloodstream. Lung tumor samples are also collected to evaluate how gemcitabine may have



Photo: Nathan Lindstrom

**Eugenie Kleinerman, M.D., conducted early studies of inhalation therapy.**

affected the tumor and the immune response in the lungs.

“We hope to find that the inhaled therapy delivers the drug directly to the lungs,” Daw says, “where it will reduce tumors while sparing healthy organs.”



## Mutation-targeting drug prolongs survival for those with a deadly type of AML

A study led by MD Anderson found the investigational drug quizartinib prolongs overall survival for patients with a deadly form of acute myeloid leukemia (AML) linked to a genetic mutation called FMS-like internal tandem duplications (FLT3-ITD).

“Currently, there are no approved targeted therapies for patients with relapsed FLT3-ITD-associated AML, which represent a significant unmet medical need,” says Jorge Cortes, M.D., deputy chair and professor of Leukemia and lead investigator of the study called QUANTUM-R. “Our findings demonstrated that patients on quizartinib alone had an estimated overall survival of 27 percent after 52 weeks of treatment compared with 20 percent for patients on standard chemotherapies.”

QUANTUM-R is the first trial to demonstrate improved overall survival for FLT3-ITD-associated AML patients who were treatment-resistant or who relapsed after prior therapy. The study followed 367 patients for 103 weeks at which time the first analyses were conducted. Minimal side effects were observed.

Cortes led the multi-institutional effort to develop and test quizartinib, a small molecule receptor tyrosine kinase inhibitor (TKI) targeting ITD abnormalities within the FLT3 gene. FLT3, a receptor tyrosine kinase commonly expressed in AML, is mutated in approximately one-third of AML patients. Tyrosine kinases are enzymes often linked to cancer as they play a critical role in cellular processes, including cell growth, division, differentiation and cell death.

“These pivotal data confirm that targeting FLT3-IT with this potent new therapy may be of significant clinical value,” said Cortes. “These results represent the first positive Phase III trial to demonstrate improved overall survival in patients with AML-associated FLT3-ITD.”

— Scott Merville

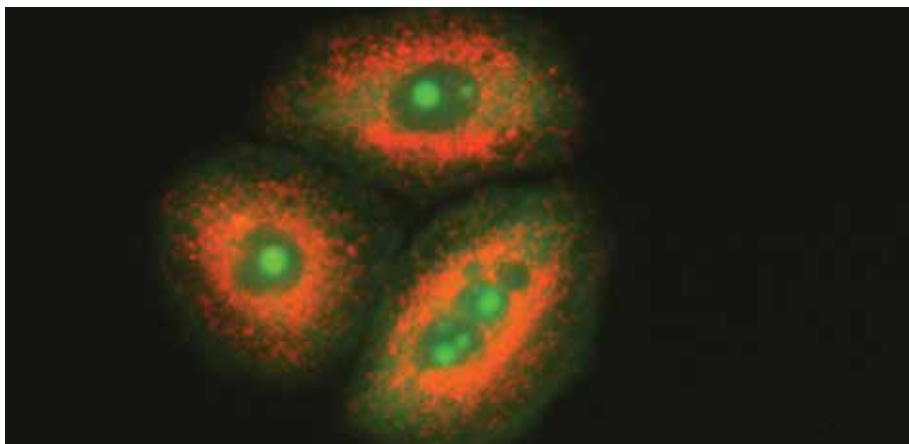


Photo: NCI

This image shows non-small cell lung cancer cells. The vast majority — 80 to 85 percent — of lung cancers are non-small cell lung cancer.

## An enemy of lung cancer immunotherapy is flushed out

Researchers at MD Anderson Cancer Center have uncovered a genetic condition that thwarts the most common immunotherapy used against lung cancer, opening new avenues for improved targeting of immune checkpoint blockade drugs and extending their use to more patients with new combinations.

Anti-PD1 or PD-L1 drugs that block an off-switch on immune system T cells, facilitating their attack on tumors, provide durable responses in about 20 percent of non-small cell lung cancer patients.

“These findings are a major step on the path to more personalized immunotherapy, where we identify targets for specific groups of patients, and tailor treatment strategies for them, just as we did with molecular targeted therapy,” says John Heymach, M.D., Ph.D., professor and chair of Thoracic/Head and Neck Medical Oncology.

Published in *Cancer Discovery*, the research paper shows that a gene called STK11 mutated or deleted in a third of non-small cell lung cancer patients, fosters an immunologically “cold” tumor microenvironment, with minimal penetration of tumors by T cells, rendering anti-PD1/PDL1 drugs ineffective.

The paper describes how adding specific types of drugs to anti-PD1 therapy might overcome resistance in these cases. The project

received vital early funding from MD Anderson's Moon Shots Program™ through the Lung Cancer Moon Shot™.

### The prime genomic driver of resistance

“We've identified what we think is the most prevalent genomic driver of a cold tumor microenvironment and primary resistance to anti-PD1 immunotherapy in non-small cell lung cancer,” says Ferdinandos Skoulidis, M.D., Ph.D., assistant professor of Thoracic/Head and Neck Medical Oncology and lead author of the paper.

“Our results suggest that a single molecular mechanism downstream from STK11/LKB1 mutations accounts for a very large percentage of patients whose tumors resist immunotherapy,” Skoulidis says, “instead of multiple mechanisms each accounting for a small fraction of patients.”

Researchers had previously identified patients who have mutations in both the tumor-suppressing STK11/LKB1 and the cancer-promoting KRAS genes as a distinct group. Working with colleagues at other cancer centers through a Stand Up to Cancer dream team grant, they tracked down the specific impact of the mutations.

— Scott Merville

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