09
fall

Moving toward a future without cancer.

momentum

IN THIS ISSUE: EXPANDING CANCER THERAPIES • YOU SURVIVED CANCER: NOW WHAT?

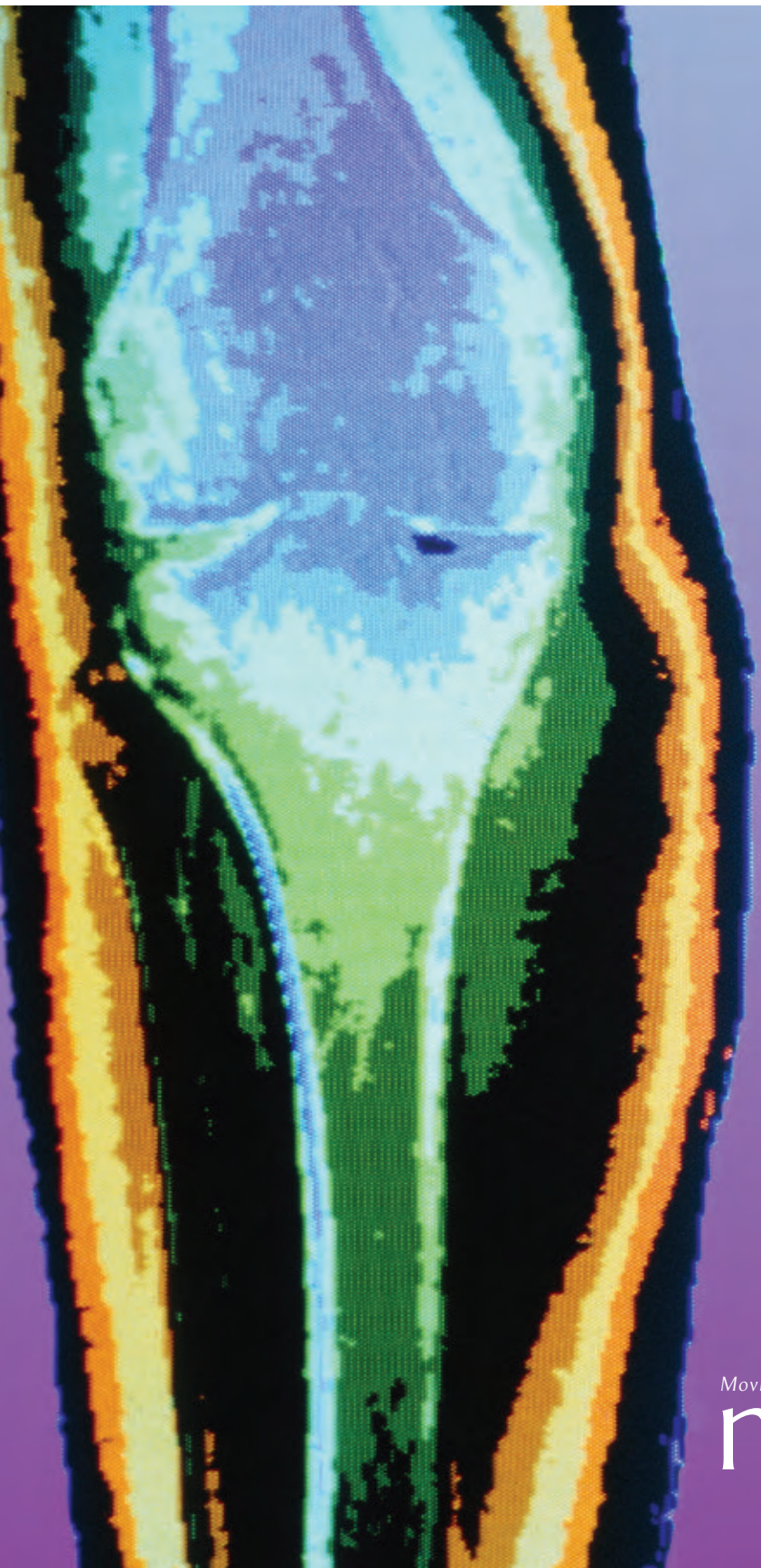
Can cancer treatment be tailored to 'fit' each patient?

On the cover:

Advances in understanding the genetic changes that drive individual tumors are now allowing researchers to "tailor" cancer therapy by "matching the right drug to the right patient at the right time." See page 8.

Pictured below:

False-color CT scan showing osteosarcoma, a malignant bone tumor (shown in green), at the head of the tibia bone of the leg just below the knee joint. Osteosarcoma occurs most frequently in children and commonly affects long bones of the leg or arm, around the knee, hip or shoulder. Credit: GCa / Photo Researchers, Inc. See page 4.



EDITOR
Melissa Marino

CONTRIBUTING WRITERS
Leslie Hast
Leigh MacMillan
Cynthia Floyd Manley
Melissa Marino
Will Peters
Kevin Plott
Dagny Stuart

PHOTOGRAPHY/ILLUSTRATION
Dean Dixon
Dominic Doyle
Mary Donaldson
Joe Howell
Anne Rayner
John Russell
Susan Urmy
Nicholas Wilton

DESIGN & ART DIRECTION
Diana Duren

VICC ASSOCIATE DIRECTOR FOR COMMUNICATIONS
Cynthia Floyd Manley

DIRECTOR OF PUBLICATIONS
Nancy Humphrey

EXECUTIVE DIRECTOR OF NEW MEDIA AND ELECTRONIC PUBLICATIONS
Wayne Wood

COVER PHOTO
Susan Urmy

EDITORIAL OFFICE
Vanderbilt University Medical Center
Office of News and Public Affairs
D-3237A Medical Center North
Nashville, TN 37232-2390
(615) 322-4747

CONNECT WITH US
on Twitter: www.twitter.com/ManleyatVICC
and Facebook: www.facebook.com/vanderbiltingram

Momentum is published twice a year by Vanderbilt-Ingram Cancer Center, in cooperation with the Vanderbilt University Medical Center Office of News and Public Affairs. The editor welcomes letters and comments from readers at the above address.

Moving toward a future without cancer.

momentum

09
fall

contents

04


24


37


32

features

departments

web link
To view Momentum online:
www.vicc.org/momentum

JOE HOWELL

Director's letter

"It is far more important to know what person has the disease than what disease the person has." – *Hippocrates*

This quote from the "father of medicine" dating back more than 2,300 years is apropos for cancer diagnosis and treatment today. Cancer is a very personal disease. Many are forever changed, often in very personal ways, by an experience with cancer and its impact – of both tumor and treatment.

For me, the fight against cancer became really personal a decade ago. Oh, I had always pictured in my mind "The Patient" who would ultimately benefit from my work. But as passionate as I had been about what I was doing, it wasn't until "The Patient" became my own father that I felt it on a personal level. Today, my father is one of 12 million Americans who are cancer survivors, and for that – and for the new perspective his experience offers my work – I am very grateful.

At the biologic level, cancers are also very personal. Cancer cells are your own cells, turned against you by genetic abnormalities, and no two tumors are exactly alike. For decades, we've been unable to take advantage of that difference in our treatments. We were left to play the odds, if you will, by choosing a treatment for one person based on how large groups of people responded in clinical trials. Now, decades of research and the sequencing of the human genome are enabling us to do things differently – to take advantage of what we know about the genetics of cancer and apply that knowledge to the individual, so that the treatments used are the most effective and least harmful to each patient based on that individual's own tumor.

In the future, we would like to be able to analyze every tumor for its specific genetic alterations or "drivers" and then be able to choose the right treatment based on that knowledge.

This approach is known as "personalized medicine," and it is gaining momentum in academic medical centers across the country. While it is being explored for many diseases, it is perhaps most evident so far in cancer care. For instance, every woman diagnosed with breast cancer has her tumor tested for expression of a molecule called HER-2/neu. If her tumor is positive, she is a candidate for Herceptin, which blocks HER-2/neu; if it is negative, she is offered another treatment. Similar genetic "profiles" are being identified to "personalize" therapy for lung cancers, melanomas, lymphomas and others.

In the future, we want to be able to analyze every tumor for its specific genetic alterations, and then choose the right treatment based on that knowledge. For that to become routine, we must discover more genetic drivers, develop efficient and scalable ways to screen for them, and have more drugs available that will be effective on tumors with specific genetic make-ups. We also want to use genetic insights to make a difference across what we call the entire continuum: from prevention through early detection, targeted treatment and survivorship care.

In this issue of *Momentum*, you'll read about several exciting new initiatives that are creating what is perhaps a unique environment in which this work can flourish. You'll meet three of our newest faculty recruits – Drs. Stephen Fesik, William Pao and Debra Friedman – and learn about their work in drug discovery, personalized oncology and survivorship research and care. The expertise and energy they bring, combined with the infrastructure and talent already in place, positions us to lead the way in both development and delivery of personalized cancer prevention, detection, treatment and survivorship care. And, as always, you'll meet interesting survivors whose stories inspire us and remind us that cancer is always personal.

Sincerely,

ACLOSERLOOK

JULIA CARTWRIGHT | Oncology Pharmacy Manager

ANNE RAYNER

JULIA CARTWRIGHT, R.PH., ONCOLOGY PHARMACY MANAGER, HAS AN INTENSE, unceasing desire to know how things work in order to make them better. In her pharmacy, that means improving patient safety by making sure that chemotherapy drugs are prepared, delivered and administered using the safest and most efficient methods available.

Cartwright – who holds bachelor's degrees in biology from Southwestern at Memphis (now Rhodes College) and pharmacy from the University of Tennessee Center for Health Sciences – came to Vanderbilt University Medical Center in 1985 to work in the general pharmacy.

Her transition to the Oncology Pharmacy, which prepares and distributes chemotherapy drugs to the entire medical center, came after volunteering there while she was still full time at the general pharmacy.

"I really loved working in oncology because of the attention to detail that was required, the safe handling requirements, and the scrutiny that orders needed from pharmacy which made the area really challenging," she said.

Chemotherapy drugs orders are sent to the pharmacy, where staff members evaluate every known factor that could influence drug effectiveness, including all laboratory results and dosing regimens. The drugs are specifically mixed for each patient in a sterile environment underneath a vertical flow hood. The drugs are double-checked by a separate pharmacist and hand delivered to the appropriate clinic or unit to ensure safety.

After just a few short years in her new specialty, Cartwright became manager of the Oncology Pharmacy in 1989. Over her career, Cartwright has seen a paradigm shift in the way hospital pharmacies operate.

"When I started working here we didn't have a computer system in the pharmacy at all. We did everything manually, from charging each and every dose of drug that was sent to the hospital patients, to typing labels on a typewriter."

Since then, hospital pharmacies have developed automated medication retrieval, barcode verification systems, and advanced drug monitoring and dosing protocols, along with a huge array of software systems for integrating these processes. These new technologies improve patient care through automation and by allowing pharmacists to draw from the enormous wealth of knowledge accumulated in databases.

Cartwright recently spearheaded the effort to move the Oncology Pharmacy into a new, more efficient 1,600-square-foot space at The Vanderbilt Clinic, a move that allows the Chemotherapy Infusion Clinic to provide greater access to care.

The new space is twice as large as the old, and though the Oncology Pharmacy moved only this May, Cartwright had been thinking of what she would do with an expanded space for years.

"Working so many years in such tight space that is not very efficient, you start developing ideas about what would be really great if you had the space and you had to set it up," she said.

One idea was the addition of an automated medication retrieval unit called MedCarousel, which increases patient safety by checking for accuracy through an advanced barcode system and database.

"I have always been interested in learning – a doer, not a 'stand-back-and-watch' kind of person," said Cartwright. "I like to know how to fix my own problems so that I don't have to wait for someone to come and fix them for me."

Cartwright also maintains an active interest in research, overseeing and organizing nearly 100 new clinical trials each year. Over the past fiscal year, the Oncology Pharmacy prepared more than 47,000 chemotherapy doses – about 4,700 (10 percent) of which were investigational drugs. The increased space could allow the Oncology Pharmacy to conduct more clinical trials.

For Cartwright, managing the Oncology Pharmacy has provided a way for her to do something she is passionate about while giving her an endless stream of novel experiences – new technologies, new investigational protocols, and now, a new facility.

"Every day that I come to work, I've learned something or I do something new. I'm not doing the same thing over and over again… I love what I do."

– by Will Peters

BUMP, SET, SPIKE.

A volleyball player aces osteosarcoma

Camille Fraser was a healthy, active 13-year-old, playing her second season of volleyball at David Lipscomb Campus School, when she began to have pain in her right knee.

A local orthopaedic clinic diagnosed her with tendonitis and Osgood-Schlatter disease, an inflammation of the knee common in active children. She was told it would get better with time and Advil. But the pain persisted.

A few weeks later, Camille took a tumble down the front steps of her house. "It wasn't like a normal trip. I totally lost control," she recalled.

Knowing a strong and fit teenager shouldn't lose control of her leg, her parents took her for an MRI. They were told something wasn't right and referred to the Monroe Carell Jr. Children's Hospital at Vanderbilt.

In an instant, Camille's diagnosis went from sports injury to cancer.

Camille had osteosarcoma, a bone tumor that is one of more than 200 bone and soft-tissue tumors that make up a family of cancers known as sarcomas. These are some of the rarest tumors in medicine, accounting for approximately 1 percent to 2 percent of all cancers diagnosed each year. They occur most often in children and young adults, but older adults can also develop sarcomas.

Camille's tumor formed at the upper end of the fibula, the small bone in the lower leg. She began chemotherapy just after Christmas in 2004, and in February 2005, had surgery to remove the top six inches of her fibula. She continued chemo until that September and has been cancer-free since.

That was not at all how Camille expected to spend her seventh-grade year, and she said the worst part was being isolated from friends who were too young to visit the myleosuppression unit.

"I usually went in the hospital on Tuesday and came out on Friday. If there were complications, I would stay until Saturday or Sunday. It was like I lived there. It got to be a routine," she said.

Her friends sent cards, sometimes 20 per day, and her grandparents would bring whatever food she was craving, even when she went on a 12-day shrimp binge.

While her father, Stuart, worked to support the family, Camille's mother, Melissa, stayed by her side.

"It's surreal and devastating, especially in a child who had been so healthy," Melissa said. "I felt like we were on a different planet. Life was so different than what everyone else was doing. You feel like you don't belong because no one knows what you're going through."

The only outward sign of Camille's illness is long pink scar on her leg, but she says she will never be the same.

By Leslie Hast | Photography by Joe Howell

"Before my treatment, I was into anything. I was crazy and loud. But I got used to being by myself and became quiet. You would think that when you're done, you're done, but the emotions are still there," she said.

Camille is back to playing volleyball thanks to a procedure called limb-sparing surgery. In this technique, patients start with chemotherapy to shrink the tumor, then the cancerous bone and soft tissue are removed and more chemotherapy follows.

Reconstruction of the skeleton can be done with allografts (bone transplants) or metal implants. The implants use a metal alloy originally engineered for fighter aircraft. They have a rough surface that bone fuses onto, and within six weeks a permanent bond has formed between metal and bone.

Though implants or allografts can return patients to their active lifestyle in a matter of months, Herb Schwartz, M.D., professor and chair of Orthopaedics and Rehabilitation, cautioned that it is not always the best option. In some cases, amputation and prosthetics are more functional.

"Limb-sparing surgery is even more complicated in children or in the peripheral appendicular skeleton because skeletal loss may cause severe limb length inequalities and the reconstruction has trouble with durability and growing with the child," Schwartz said. "In tough cases, sometimes the function of the limb is worse with limb-sparing surgery than with amputation."

In Camille's case, the fibula was an "expendable" bone, and she had no reconstruction. "Her function without it is better than anything we can construct in its place," Schwartz explained.

Another worry is the durability of the metal implants, and Ginger Holt, M.D., assistant professor of Orthopaedics and Rehabilitation, is performing research to determine how long they will last.

"If you put metal in, you get back function much quicker (two to three months), but since it's not biologic, it's more likely to fail at 15 to 20 years out," Schwartz explained. "The converse is if you replace it with an allograft. It could take you a year or more to have it grow together to a point where it is strong enough to support your weight. So you're spending a year or two on crutches, but 10 to 12 years from now, you're better off because you're not going to need as many surgeries in the future."

Three orthopaedic surgeons at Vanderbilt now practice full-time orthopaedic oncology, and it is quickly becoming a major center for sarcoma surgery.

"I know there's a small group of people, probably only 50 people in the country who practice full-time orthopaedic oncology, and we have three of them at Vanderbilt," Schwartz said. Last year, 250 sarcoma surgeries were performed, and that number grows annually.

But successful sarcoma treatment requires a team effort from oncologists, radiologists, pathologists, nurses, therapists and social workers, in addition to surgeons.

Scott Borinstein, M.D., Ph.D., assistant professor of Pediatrics and Pediatric Hematology-Oncology, is working to establish a sarcoma program that will provide comprehensive care to patients with bone tumors.

"The goal is to coordinate the treatment and management of these complex patients, so families and patients have a better feeling that we're using a team approach," he said. "Even though I'm fairly early in my career, I've found that a multidisciplinary approach is optimal for everyone involved. All understand the treatment plan, it goes smoothly, and the end result is better care for all."

A team approach is also crucial in research. Because sarcoma is so rare, it can be difficult to recruit enough patients for a valid clinical trial. Vicki Keedy, M.D., assistant professor of Hematology/Oncology, said there can sometimes be as many as 50 to 60 centers involved just to complete one study.

"If you look at the basic science of the cancers, there's some great research going on, but it may be in a very specific subtype of sarcoma, such as synovial cell sarcoma. It's so hard to take that basic science research and put it into clinical trials because there are so few patients and so many different sarcomas. What we end up doing is getting a promising drug from synovial cell sarcoma research and testing that in all soft-tissue sarcomas. But that drug is never going to bring the outcome we would expect because the tumors are not all the same," Keedy said.

A resource that could speed advances is Vanderbilt's tissue archives. Instead of waiting for new sarcomas cases to develop, researchers can delve into tissue archives dating back to the 1920s and a tumor registry that began in 1950.

Cheryl Coffin, M.D., Goodpasture Professor of Investigative

(Left to right) Camille at her brother's 4th grade play, with her friend Alex; during her last chemo treatment with one of her nurses at Monroe Carell Jr. Children's Hospital at Vanderbilt; and helping to build a house for a family in need near Tegucigalpa, Honduras, during a mission trip.

It's a pretty exciting time for Camille Fraser. She made the first-team all-district in volleyball last year and is in the midst of her senior season.

Pathology, said Vanderbilt has just begun to revisit these archives to define what is there and how it can be used.

"Sarcomas are rare, so getting a sufficient number of either pathology samples or patients with sarcoma can be challenging. At Vanderbilt, we're fortunate to have tissue archives," Coffin said. "We may or may not be able to access medical records from decades ago. We may only have a name, birth date, a diagnosis and some slides, and we may not be able to even get that much. But even limited information combined with the tissue archives is a valuable resource for future clinical and translational research. Over time, we can determine what tests a sample is good for and what may not be feasible."

Borinstein is using the tissue archive for his research in Ewing sarcoma, a bone and soft-tissue tumor that most often occurs in adolescents and young adults. He is interested in DNA methylation, an epigenetic mechanism (chemical modification to DNA that does not change the underlying sequence) that can control the way genes are expressed.

"Research has shown that DNA methylation can occur abnormally and lead to the silencing of signals that normally prevent cells from becoming cancers," he said. "We have learned how to examine methylation patterns in old, archived tissue specimens, which is critical when investigating rare tumors such as Ewing sarcoma. We may identify methylation patterns to help us understand the cause of Ewing sarcoma, which may help us come up with better treatment strategies."

It is research like this that leads Coffin to believe that sarcoma is on the threshold of really significant advances being made in the next few decades, and Vanderbilt is poised to lead the charge.

"At Vanderbilt, we're really lucky because we have a very large group of people who can form a sarcoma team. The clinical care for sarcomas is great, and we can start to build a sarcoma program that is multi-disciplinary, that can have not only the clinical care, but also clinical and translational research and perhaps basic research. It's a pretty exciting time to be at Vanderbilt," she said.

It's a pretty exciting time for Camille Fraser too. She made the first-team all-district in volleyball last year and is in the midst of her senior season. She still has a lot of pain in her leg and sometimes has to sit on the sidelines, but her love for the sport keeps her going and her coaches and teammates are understanding.

"I wear a brace, and players will come up and ask how I messed up my knee, thinking it will be an ACL or something," she said with a laugh. "When I tell them, their eyes get really big and they say they're so sorry, but I don't mind talking about it."

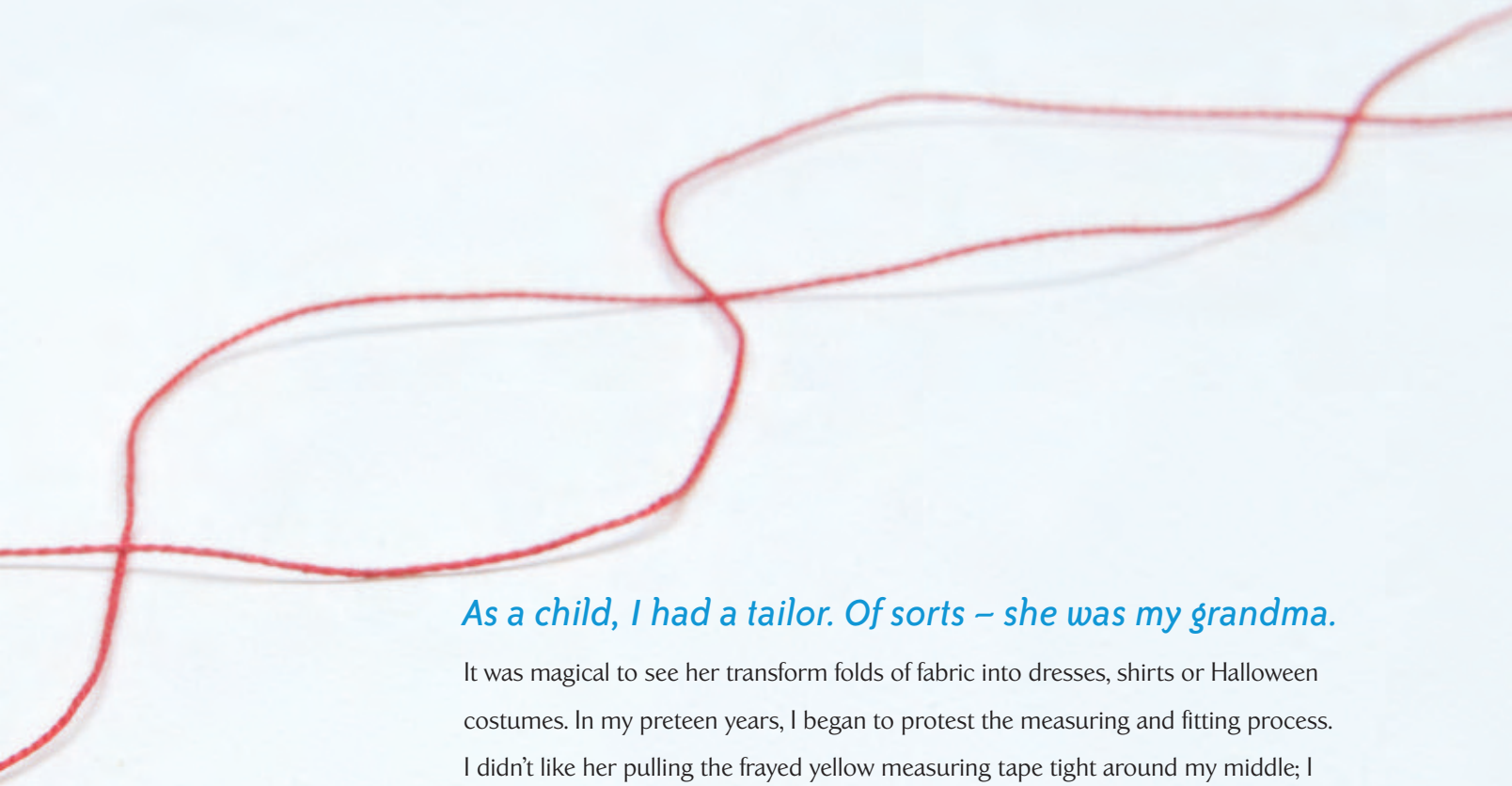
She wants to become a child life specialist to help reduce the stress and anxiety of other children facing similar experiences. Camille has already made two mission trips to Honduras and definitely plans on returning next summer to continue her work.

"We build houses, deliver food packages, visit orphanages, just do what needs to be done. I would move there right now if she would let me," she said, pointing to her mother. "As much as I have gotten, I have to give back."

a perfect fit

Cancer medicines get personal(ized)

By Leigh MacMillan | Photograph by Susan Urmy



As a child, I had a tailor. Of sorts – she was my grandma.

It was magical to see her transform folds of fabric into dresses, shirts or Halloween costumes. In my preteen years, I began to protest the measuring and fitting process. I didn't like her pulling the frayed yellow measuring tape tight around my middle; I grumbled when the straight pins poked me as she adjusted a partly sewn garment. But my objections evaporated when the dressing room mirrors revealed time and again that my arms and legs had grown too long for the "standard" clothes in my size. Not so with the outfits grandma made for me. Each one was a perfect fit.

Can cancer treatments be tailored like clothing? Can the medicine be matched to "fit" each patient? Increasingly, the evidence is saying yes – cancer treatments can be tailored when tumors have specific genetic changes that are driving their growth, and when drugs exist that counteract those signals.

Simply put, personalized oncology means

"matching the right drug to the right patient at the right time," says William Pao, M.D., Ph.D., who is leading the new Personalized Cancer Medicine Initiative at the Vanderbilt-Ingram Cancer Center.

Within the next year, Vanderbilt-Ingram aims to make personalized cancer medicine a routine part of clinical care. Starting with lung cancer and melanoma, Pao and his colleagues will wrap their genetic measuring tapes around every tumor – and select therapies that fit the specific genetic changes they find.

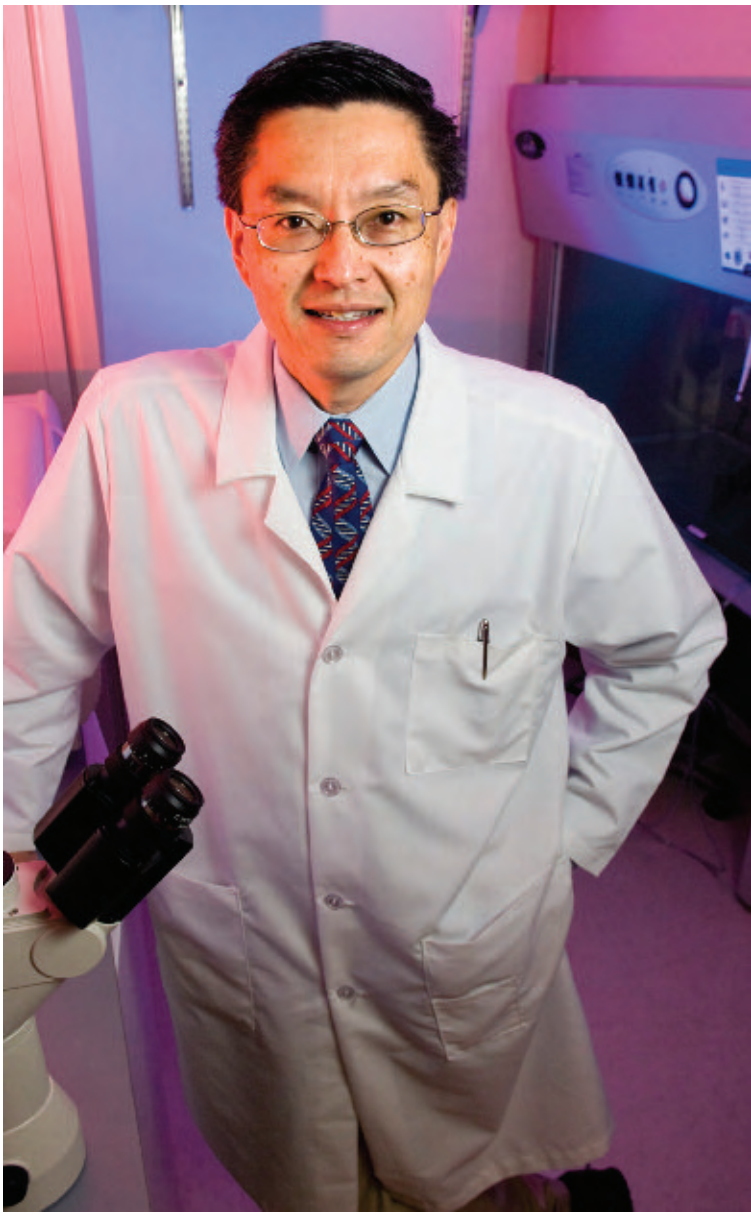
Off-the-rack treatments

Surely cancer care has always been personalized, you might be thinking. And to the extent possible, it has been. Oncologists take into account the patient's characteristics and the cancer's characteristics (tissue type, stage) to plan therapy.

But it's not an exact science. Chemotherapy treatments are often a one-size-fits-all approach – sometimes they work, and sometimes they don't. In general, patients receive a course of chemotherapy and then wait – up to six weeks or longer – to find out if the drug is having an effect. If it doesn't appear to be killing the cancer cells, the doctor and patient will decide on another treatment option. In the meantime, the patient may have suffered the unpleasant side effects of chemotherapy, without any benefit.

Rita Quigley knows this approach first-hand.

In the summer of 2007, she noticed a small bump, the size of a mosquito bite, under the skin on her upper arm. She mentioned it to the dermatologist she was routinely seeing because of a malignant melanoma (skin cancer) that had been removed from her back 17 years earlier. There was nothing visible on the skin, and the dermatologist had trouble even feeling the bump, Quigley recalls. Her family physician suggested it might be a sebaceous cyst.



SUSAN URMY

William Pao, M.D., Ph.D., is leading Vanderbilt-Ingram's new Personalized Cancer Medicine Initiative.

Quigley requested that the mass be removed. The pathology report came back with ominous news: melanoma.

CT and PET imaging scans revealed that she had tumors in her lungs, and Quigley's Huntsville, Ala., oncologist referred her to Jeffrey Sosman, M.D., director of Vanderbilt-Ingram's Melanoma Program.

Malignant melanoma that has metastasized to distant sites in the body is notoriously difficult to treat.

"Melanoma has been the most frustrating of solid tumors," Sosman says. "There have been some positive results with various therapies in a small minority of patients, but the great majority of patients do not respond to the chemotherapy or immunotherapy treatments that we have."

Sosman opted to treat Quigley with the chemotherapy drug dacarbazine. She came to the clinic for an intravenous infusion once every three weeks for three months, but the tumors in her lung didn't shrink. She says she was fortunate to only suffer mild discomfort – achiness and flu-like symptoms – during the chemotherapy.

At the end of October 2007, thoracic surgeon Eric Lambright, M.D., at Vanderbilt-Ingram removed her lung tumors. The surgery was successful, and she recovered from it.

But a follow-up scan several months later showed new tumors in Quigley's pelvic area, and Sosman decided to treat her with interleukin-2, an immunotherapy aimed at stimulating the patient's immune system to kill the cancer. For the interleukin-2 treatment, Quigley was hospitalized for five days while the medicine was administered every eight hours around-the-clock through a central venous catheter. After one week of rest at home, the treatment was repeated. Hospitalization is required because the side effects of interleukin-2 treatment can be severe.

"Interleukin-2 is a different ballgame. It was several weeks after the second treatment before I felt like myself again," Quigley says.

Six weeks after the treatment, imaging scans showed no tumor shrinkage.

It had now been a year since Quigley had noticed the bump on her arm. She had been through two surgeries, two grueling treatments, and still the cancer persisted.

But at this point a door opened for her – Sosman and his Vanderbilt-Ingram colleague Igor Puzanov, M.D., were studying a new drug in patients with metastatic melanoma. The study was a Phase I clinical trial, meaning that the drug had passed through pre-clinical (cell and animal) testing, but was just beginning to be tested in patients. The drug was not "off-the-rack" – instead it was tailored to a particular genetic change in tumor cells, and Quigley's cancer had the genetic change. She enrolled in the trial.

Measuring cancer genes

To understand the experimental drug being offered to Quigley – and others like it – we need to back up.

For more than 30 years, cancer has been linked to genetic mutations that give cancer cells a growth and survival advantage. As the thinking goes, tumor formation involves multiple genetic

Trying on new cancer drugs

Lee Lange has a Nike-inspired message for patients who are on the fence about participating in a clinical trial: just do it.

Lange, who taught high school biology at Fort Campbell, Ky., for 37 years, sees his own participation – he's currently taking part in his second study for patients with melanoma – as a positive contribution to science.

"I'm proud to do it," says Lange, a patient of Jeffrey Sosman, M.D., director of the Melanoma Program at Vanderbilt-Ingram Cancer Center. "I'll take any protocol I'm offered because I know that even if it doesn't help me, the doctors are getting information that will help someone else down the line. And that's what science is all about."

"The willingness of patients to help themselves and others by participating in trials is so critical to our efforts to further clarify and improve the treatment of melanoma," Sosman says.

Vanderbilt-Ingram has recently expanded its Phase I Drug Development Program with newly dedicated clinical space and new leadership. Jordan Berlin, M.D., associate professor of Medicine, will direct the program, and Igor Puzanov, M.D., assistant professor of Medicine, will serve as associate director.

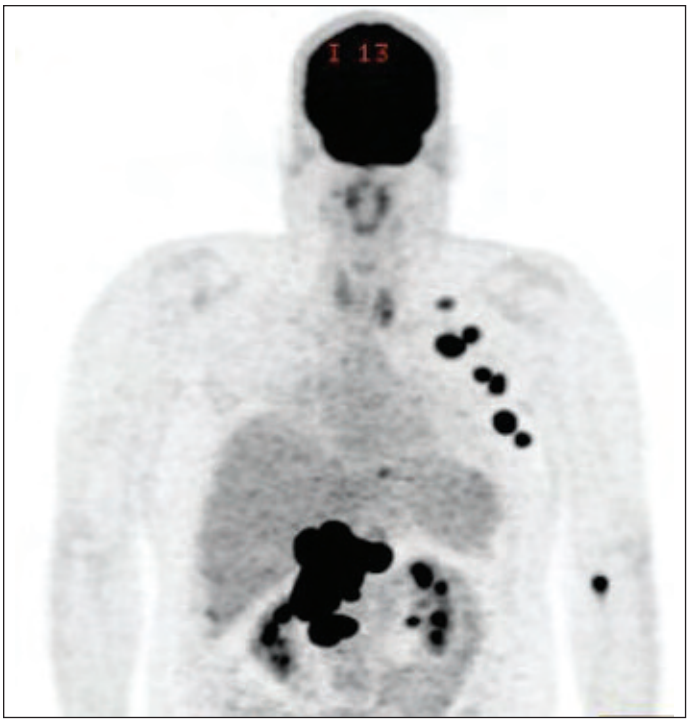
In the Phase I Program, researchers test new anti-cancer compounds in a small group of people for the first time. They evaluate safety, determine dosage and identify side effects. Phase I trials are not usually designed to test drug effectiveness. But with the advent of targeted drugs and the ability to "tailor" these medicines to selected patients, it may be time to re-think some strategies of Phase I studies, Sosman says.

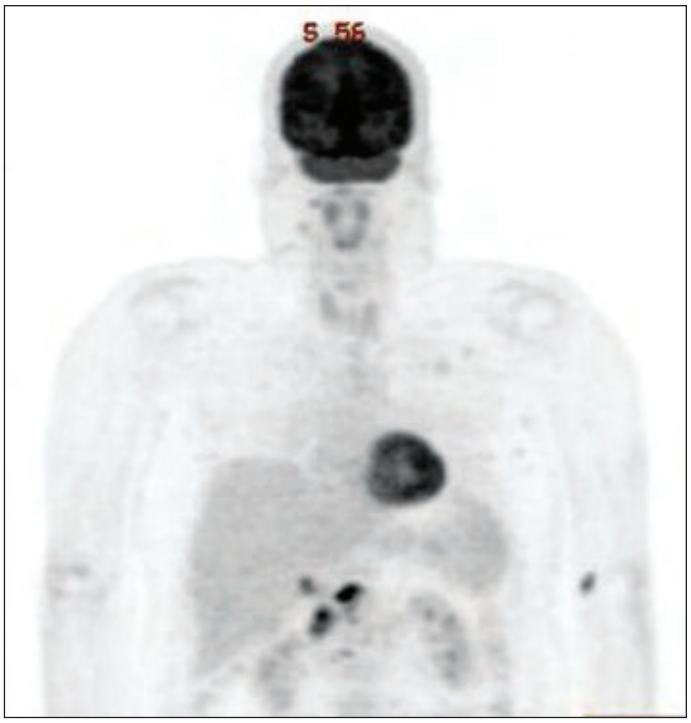
"I think we need to make the greatest effort to match the drugs to the tumor's genetic changes – and perhaps even as early as in a Phase I trial."

– by Leigh MacMillan

web link

For more information about clinical trials at Vanderbilt-Ingram, please visit www.vicc.org/ct





In this PET scan, dense black spots in the chest and abdomen represent melanoma metastases before treatment (left) and after treatment with experimental "tailored" drug PLX4032 (right). Images courtesy of Jeffrey Sosman, M.D.

mutations in a single cell – some that activate growth-enhancing genes (oncogenes) and others that inactivate growth-inhibitory genes (tumor suppressor genes).

Recently, investigators and the pharmaceutical industry have aimed drug development efforts at these mutant gene products that contribute to cancer cell growth, with the hope that medicines "targeted" at these molecules will kill cancer cells without harming normal cells. But how likely is it that blocking just one target – when tumor cells often have many mutated genes – will kill the cancer?

Consider Gleevec. The drug bounded onto the world stage in 2001, with accelerated approval from the Food and Drug Administration for the treatment of chronic myelogenous leukemia (CML).

The genetic abnormality that causes CML – the so-called Philadelphia chromosome (named for the city in which it was discovered) – results from a translocation, a rearrangement that fuses two genes from different chromosomes together. One of the genes encodes a cellular signaling protein (ABL, a tyrosine kinase), which is usually turned "on" and "off" in a well-controlled manner. The rearrangement produces an abnormal protein (BCR-ABL), which is stuck in the "on" position and drives cells to become leukemic. Gleevec blocks the activity of the aberrant receptor, and kills the cancer cells.

The drug is effective in the overwhelming majority of CML patients with the Philadelphia chromosome, Pao notes.

"Gleevec is really the poster child of personalized cancer medicine," he says. "There's a genetic change that leads to an aberrant signaling protein and causes CML. You give the patients a pill that inhibits the activity of that protein, and the tumor cells go away."

At about the time that Gleevec was starting to work in patients with CML, Pao was a research fellow in the laboratory of Harold Varmus, M.D., at Memorial Sloan-Kettering Cancer Center. (Varmus and J. Michael Bishop, M.D., won the 1989 Nobel prize for their discoveries that oncogenes are actually cellular genes involved in normal cell growth and division, and that disturbances in these genes can lead to cancer.)

Pao and colleagues were exploring the same question that was being tested with Gleevec in CML – can tumors become so dependent on a single mutant growth-enhancing signaling protein that disrupting that signal kills the tumors? Their model was lung cancer. They had shown in mice that turning on a mutant oncogene in the lung caused lung tumors, and turning the oncogene off

caused the tumors to die. The studies supported the concept of "oncogene addiction" – a phrase coined by the late Bernard Weinstein, M.D., to describe an apparent dependency of some cancers on one or just a few mutant genes.

As they worked to understand the molecular signaling in the mouse lung tumors, Pao and colleagues (and other investigators around the country) were also testing two targeted therapies – Iressa and Tarceva – in patients with lung cancer, the leading cause of cancer-related death in the United States.

The timing was fortuitous.

Most of the patients had no response to the drugs, but about 10 percent of the patients had a rapid and sometimes dramatic clinical response.

"In some patients, within five days we could see evidence of tumor shrinkage," Pao recalls. "It looked just like this phenomenon of oncogene addiction that we were studying in the mice, and it said to us that these pills must be turning off something that's critical for the tumor. We just had to figure out what that was."

The Varmus group and others, including David Carbone, M.D., Ph.D., and colleagues at Vanderbilt-Ingram, focused on Iressa and Tarceva's molecular target, the epidermal growth factor receptor (EGFR). They found activating mutations in the EGFR gene in lung tumor tissue from patients who responded to Iressa or Tarceva.

Subsequent trials have shown that patients whose tumors have certain EGFR gene mutations have a 75 percent chance of having their tumors shrink when they are treated with EGFR-targeted medicines – oral pills with relatively mild side effects compared to chemotherapy. (These medicines are effective in only about 10 percent of "unselected" lung cancer patients.) By contrast, patients treated with standard chemotherapy have a 20 percent to 30 percent chance of tumor shrinkage, Pao says.

Pao and others have also identified genetic changes that predict that a patient will not respond to Iressa or Tarceva. And they have discovered changes that occur in tumors that are initially responsive but then become resistant to therapy.

Now the race is on, Pao says, to catalog the genetic defects in all kinds of cancers, discover which mutations are critical to tumor survival, and link those mutations to specific targeted therapies.

In the fitting room

In 2002, investigators reported that about 60 percent of melanomas contained a single mutation in a gene called BRAF. The BRAF protein functions in a cell growth signaling pathway, and the mutation activated the pathway and caused cells in culture to behave like tumor cells.

"Everyone who read that paper said, this is a target for melanoma – if we can target BRAF, we're going to see Gleevec-like responses in melanoma," Sosman recalls.

A drug called Nexavar targeted a related RAF protein and was already in clinical trials (and has since been approved) for kidney cancer. As a single agent in patients with melanoma that had resisted

The fabric of personalized cancer medicine

Scientists were still busy at work mapping the human genome back in 1997, when the creation of the Robert J. Kleberg, Jr. and Helen C. Kleberg Center for Cancer Genetics and Genomics was first announced.

Completion of that ambitious project was years away, but scientists at Vanderbilt-Ingram were already looking to answer the next question: what do all these genes actually do?

Today, with the help of the Kleberg Foundation, Vanderbilt-Ingram Cancer Center scientists are poised to take the next step in this journey: to leverage knowledge of the genetic and molecular drivers of cancer and technological advances in imaging and other disciplines to detect cancers early and to precisely match effective treatments to the patients in whom they will work best.

The new name for the center –the Robert J. Kleberg, Jr. and Helen C. Kleberg Center for Personalized Cancer Medicine – reflects not only groundwork of the foundation's earlier support but the promise of future impact in cancer detection, treatment, prevention and survivorship care.

"We applaud Vanderbilt-Ingram Cancer Center's groundbreaking research and their many successes, and we are pleased to expand our partnership with them in a way that can improve the lives of so many patients and families affected by a cancer diagnosis," said Helen Alexander, vice president of the San Antonio-based foundation.

Such investment by private philanthropists is critical, says Jennifer Pietenpol, Ph.D., director of the Vanderbilt-Ingram Cancer Center. "In today's climate, government and industry are more reluctant than ever to take big risks, but it will take risks to make the kinds of giant leaps in cancer detection and treatment that we all want to make and that the public rightly demands."

Over the years, Kleberg Foundation support totaling more than $12 million has enabled Vanderbilt-Ingram to recruit some of the best and brightest and to accelerate analysis and correlation of molecular features of tumors with clinical outcome. Recent findings include identification of a gene signature that may help predict outcome in certain types of breast cancer and discovery of a new molecule that might be used to put the brakes on a common type of head and neck cancer.

– by Cynthia Floyd Manley

JOHN RUSSELL

Jeffrey Sosman, M.D., and colleagues are studying a new chemotherapy drug tailored for melanomas with a specific genetic alteration.

other therapies, it "didn't do much of anything." Another few drugs that worked in the same pathway, but not on BRAF, showed some activity, but the overall results were discouraging, Sosman says.

And then along came PLX4032, a BRAF inhibitor produced by Plexxikon and Roche Pharmaceuticals that in cultured cells specifically blocked the BRAF mutant most commonly found in melanoma. Puzanov led Vanderbilt's participation in the Phase I trial (which has ultimately included six centers).

Initial results were not stellar, Sosman recalls, but a reformulation of the drug allowed the investigators to achieve higher doses and "all of a sudden, everybody started seeing responses." He remembers the striking images that investigators at the various centers shared electronically.

"It was really stunning. Some of the patients were responding incredibly quickly, and we even saw symptomatic improvement – patients who were sick when they started, got the drug, and felt much better. That's something I've never seen in treating patients with melanoma," Sosman says.

Rita Quigley started taking PLX4032 in August 2008. Her tumors have shrunk, and she continues to take the pills daily, with minimal side effects. She felt well enough to return to work as a part-time nurse in a pediatrics practice, after seeing her second of three daughters off to college.

She has the highest praise for Sosman and his colleagues and finds it "amazing that it's a possibility" to have a medicine selected to fit her tumor.

"I feel very blessed; I'm very thankful," Quigley says.

Puzanov presented initial findings from the Phase I trial at this year's annual American Society of Clinical Oncology conference. Of 16 patients with BRAF-positive melanoma, more than half had their cancer shrink by at least 30 percent. Patients without the mutation had no response to the drug. The investigators have extended the Phase I trial to include additional patients, and they are preparing to launch Phase II studies, which will treat between 90 and 150 patients at 12 centers. Sosman is leading the Phase II trial.

"The world of melanoma treatment has changed," Sosman says. "It's really very exciting to treat patients whose tumors have the right genetic profile with this drug and expect them to respond, and for the most part they do."

The BRAF mutation targeted by the PLX drug also is present in other cancers, Sosman points out. It's present in about 40

"The pace of discovery is increasing and we're going to be able in the next five to 10 years to routinely assign therapies based on the genetic makeup of patients' tumors."

percent of thyroid cancers, 10 percent to 15 percent of colon cancers, and 3 percent to 6 percent of lung cancers. A trial under way in colon cancer patients with the mutation is showing response rates similar to the melanoma studies.

These findings highlight a shifting view of cancer – rather than being a disease known primarily by its tissue of origin (breast, colon, lung), it is moving to a disease classified by the genetic mutations that drive it. And this change has implications for therapy, Sosman notes.

"Cancers of the same genetic abnormalities should be treated the same whether they come from the skin or the colon or the lung," he says. "I think that's a concept that is really going to change our approach to treatment."

This is the crux of the personalized oncology initiative that Pao is leading at Vanderbilt-Ingram – to put into place the systems that will allow physicians to routinely measure a tumor's genetic changes and fit therapies to them.

Stitching the pieces together

Implementing a new clinical strategy requires the cooperation of multiple parts of the clinical enterprise, Pao points out, which could be an onerous task. But at Vanderbilt-Ingram, which he joined this year, Pao has found a culture of collaboration and "an openness to new ideas and trying new things that might improve patient care."

With the aid of Cindy Vnencak-Jones, Ph.D., and colleagues in the Department of Pathology's Clinical Molecular Genetics program, Pao is developing a platform to test for multiple genetic mutations at the same time.

The goal is to develop tests for between 30 and 50 mutations. Pao and colleagues are "mining" databases of reported mutations, in order to build melanoma- and lung cancer-specific panels. Tested mutations will have relevance with respect to existing or emerging targeted therapies. Later, they will develop panels to detect mutations specific to other cancer types.

The results of the tests will need to be integrated into the electronic medical record with algorithms that aid physicians in assigning therapies. Vanderbilt is a world leader in medical informatics, and Dan Masys, M.D., professor and chair of Biomedical Informatics at Vanderbilt, and his colleagues are working on the informatics needs.

"Many cancer centers are trying to move this kind of tumor genotyping and therapy planning forward, but the big question is how to do that in the most efficient manner," Pao says. "I think that Vanderbilt has the right strengths to really make this happen."

The initiative is being supported by the Robert J. Kleberg, Jr. and Helen C. Kleberg Foundation and an anonymous foundation. Foundation support is especially important, Pao says, because it is difficult to gain National Institutes of Health funding for "nuts and bolts" implementation efforts like this.

Ultimately, Pao thinks that using genetic measurements to guide therapy decisions will become routine, something that we won't even call "personalized" anymore.

But he is quick to acknowledge that we're not there yet.

We still need the results of ongoing efforts that are defining the genetic mutations in cancers – particularly those mutations to which tumors become "addicted," Pao says. We need more and better drugs to hit those targets. We need to understand how tumors that initially respond to targeted medicines become resistant – something Pao and his colleagues have done for lung cancers that become resistant to Iressa or Tarceva – and use that information to identify new targets and new drugs.

Despite the hurdles, Pao is excited.

"The genetic alteration that causes CML – BCR-ABL – was discovered more than 30 years ago, but it wasn't until the last decade that we had a drug that could be used in patients with that mutation," he notes. In contrast, investigators identified a new genetic mutation (called EML4-ALK) in 5 percent of lung cancer patients just two years ago, and already a specific inhibitor has moved through Phase I trials with a 50 percent response rate in patients with the mutation.

"The pace of discovery is increasing and we're going to be able in the next five to 10 years to routinely assign therapies based on the genetic makeup of patients' tumors."

Perfectly fitted therapies. My grandma would be pleased.

More on the menu

Expanding the selection of cancer therapies

By Melissa Marino | Photograph by Susan Urmy

With the promise of personalized cancer medicine comes an unsettling question:

Even if we know the genetic profile of a patient's tumor, do we have the corresponding therapies to treat it effectively?

Right now, probably not.

The online "Catalogue of Somatic Mutations in Cancer" lists more than 80,000 mutations in more than 13,000 genes that have been linked to cancer.

Currently there are only a few dozen targeted cancer therapies approved and in clinical use – many of them targeting the same biological pathway. And of the hundreds undergoing clinical trials, only one or two new drugs are approved each year.

That leaves a wide array of cancer-associated mutations without corresponding targeted therapies – and a lot of patients without the benefit of tailored treatment options.

"Recent advances in identifying the molecular drivers of some cancers allows us to more precisely predict who will benefit or not benefit from certain treatments," says Jennifer Pietenpol, Ph.D., director of the Vanderbilt-Ingram Cancer Center. "But now, we need to understand those drivers for each and every tumor and have a wide menu of options to choose from so that each patient can benefit from this kind of precision."

Drug discovery and development was once the exclusive realm of the pharmaceutical industry. And industry is certainly still critical in expanding the selection of new targeted cancer therapies. But academic institutions are becoming increasingly important in the discovery and development of drug candidates.

Academic centers should not only generate basic discoveries about cancer biology, "but then take that next step toward trying to use that information in a fashion that will benefit patients," says Larry Marnett, Ph.D., director of the Vanderbilt Institute of Chemical Biology, which is focused on applying chemical approaches to biological problems – such as drug discovery.

Researchers at Vanderbilt-Ingram and across the Vanderbilt campus are taking that next step to fill the menu with new drugs to offer those choices – for patients and their physicians.

No "one size fits all" for cancer

Drug discovery in oncology is plagued by one obstacle that most other diseases are not – the fact that cancer is not one disease but many.

"If someone says, 'I have cancer,' that's almost like saying 'I'm sick.' It's not defining the disease," says Stephen Fesik, Ph.D., professor of Biochemistry and Pharmacology.

Cancers are driven by a host of genomic and cellular alterations – simple mutations, and chromosome rearrangements, amplifications and deletions, resulting in changes on the protein level. Even if two people have the same "tissue" type of cancer (for example, breast cancer), there may be different genetic factors driving their tumors.

"One person's breast cancer can be very different from another person's breast cancer, caused by very different mutations and genetic alterations. And while one patient may respond to one therapy, another breast cancer patient may not," Fesik says.

"That makes it very difficult to treat because (the cancers) are not the same. It's not the same target, not the same problem."

And even within an individual's tumor, one tumor cell may harbor vastly different mutations than its (also malignant) next-door neighbors.

"Heterogeneity is THE challenge with cancer versus other diseases," Fesik says.

The mind-boggling complexities of cancer biology make it difficult to find treatments that are effective for all – or even most – patients.

"You might look at all that and say 'This is impossible. How are you going to target it if all the targets are different, they vary between and within different patients…and over time, as resistance pops up?' It seems impossible."

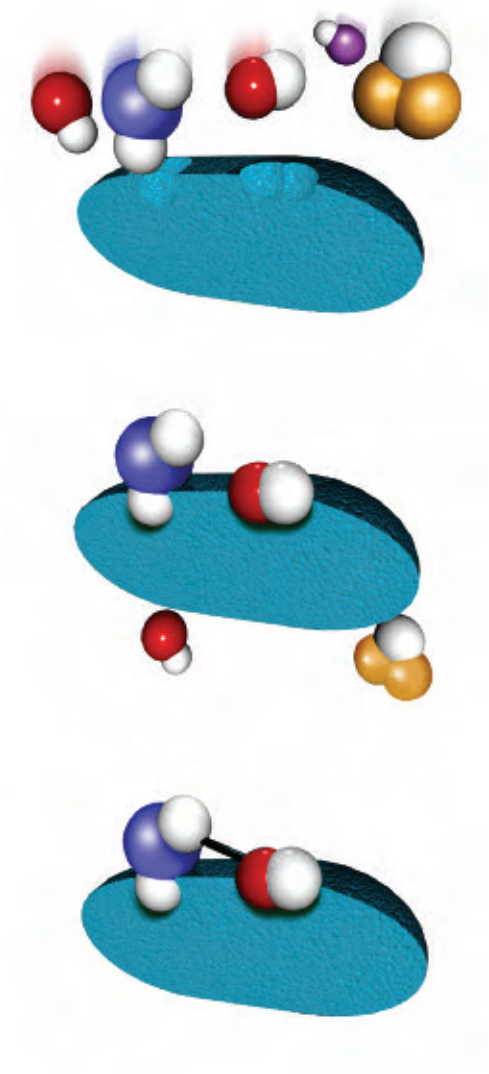
Drugging the undruggable targets

Ready to take on this challenge, Fesik left Abbott Laboratories this year to come to Vanderbilt to lead the cancer drug discovery initiatives of the Vanderbilt-Ingram Cancer Center and the Vanderbilt Institute of Chemical Biology. As Abbott's divisional vice president of cancer research from 2000 until his departure, he was responsible for building a pipeline

Drug building

One piece at a time

Illustration by Dominic Doyle



In fragment-based drug design, a library of drug "fragments" (top panel) are screened to find fragments that bind to "subpockets" on a target protein's binding surface (middle panel).

NMR spectroscopy or X-ray crystallography provides a 3-dimensional structure of the protein binding to the drug fragments, showing how the fragments fit into the protein's binding pocket and how they might be linked together.

The fragments are then linked together and assembled into a larger molecule that better fills up the target protein's binding pocket (bottom panel).

of drug candidates with promising anti-cancer activity.

He knows the industry – and he knows drugs.

He also knows that industry alone can't make the advances in cancer therapy that the half-million Americans who die each year of the disease need.

"Industry is looking more and more on the outside for their innovative drug molecules," he says.

Using a technique he pioneered while at Abbott Laboratories – fragment-based drug design – he believes he can help fill up the therapeutic menu with candidate compounds that could make enormous strides against cancer.

"If we really want to see a change in how we treat cancer patients, we need to take risks. We need to go after these extremely difficult, challenging targets – but targets that make sense based on cancer biology," Fesik says.

He's not interested in making incremental improvements to existing drugs. His sights are set much higher.

"My interest is to develop therapies that will have a dramatic effect on cancer patients," he says. "Not simply trying to change a drug that is currently given twice a day to once a day, or to eliminate a slight side effect … I'm looking for the cures. Not the extension of one month or two months, but actual cures."

As formidable as the problem is, Fesik's strategy is relatively simple.

Even though there are many different genetic alterations that drive tumors, there are some common themes and pathways that all or most cancers rely on to survive. This includes processes like angiogenesis (the growth of new blood vessels) and cell survival mechanisms (which keep tumor cells alive when the body would normally cause them to self-destruct).

The goal, Fesik says, is to develop drugs that act on highly validated targets within these common pathways known to be critical in many different cancers.

So, once you have identified that a particular pathway is altered in a particular cancer, you can develop pathway specific inhibitors and have something with which to treat the cancer.

"And that will be the mainstay of cancer treatment," he explains. "You might say 'That seems like a simple idea. Why doesn't everybody do that?'"

The main problem is that many of these targets are considered "undruggable" by traditional methods, says Fesik. "It is very difficult to find a small molecule that's going to bind to these targets and affect their function."

Stephen Fesik, Ph.D.

THE FACTORY PHOTOGRAPHY BY GOLDY LOCKS

Putting together the pieces

Fesik believes he knows how to overcome the problem of the "undruggable" target – by building drugs one small piece at a time.

The traditional approach to drug design involves the screening of a library of relatively large (at least on the chemical scale), intact compounds against the desired protein target, which has cup-like "pockets" to which drugs bind and can interfere with their activity. Then chemists make similar compounds – analogs – to try to find a molecule that will fit best into the binding pocket and affect the protein's activity.

But a key limitation in this strategy is the limited numbers of existing chemical compounds that can be tested. So Fesik is taking a slightly different path to the final drug molecule.

Instead of altering the large, intact lead molecule, Fesik's approach – fragment-based design – is to screen for fragments or pieces of that ultimate molecule and link them together, like Tinkertoys.

Once a high-throughput screen identifies chemical fragments that bind to "subpockets" on the target protein's binding surface, the 3-dimensional structure of the protein binding to the drug fragments is determined with NMR spectroscopy or X-ray crystallography.

The 3-dimensional structures provide a picture of how the fragments fit into the protein's binding pocket – and how they might be linked together.

The fragments can then be assembled into a larger molecule that better fills up the target protein's binding pocket.

"It's a modular approach to drug discovery. In principle, it's like screening a much larger library of compounds," explains Fesik. "And you're tailoring the molecule for binding to the protein."

This method, he says, "is a great way to create molecules that have never been made before and therefore would not have been found in a traditional high-throughput screen."

And clinical trials are now bearing out the utility of this strategy. A drug candidate that targets a protein (called Bcl2) involved in programmed cell death (apoptosis) – which Fesik developed at Abbott using fragment-based drug design – is now entering Phase II clinical trials and showing promise against some lymphomas, leukemias and other cancer types.

"It's a great strategy," says Marnett. "The targets he is going after are ones that others have tried and failed. This is exactly the kind of thing we should be doing."

Having an industry-like drug development capability – and the expertise of a leader in the field of drug discovery – will also help other Vanderbilt cancer researchers take their findings about drug targets a step beyond what had been previously available in academia.

Marnett's lab, for example, has identified a molecule that helps cancer cells ward off toxic stressors like chemotherapy. Cancer cells tend to evolve ways to escape the body's natural immune defenses that would otherwise kill them off. Marnett's target is, interestingly, a chaperone protein that binds to the Bcl2

Stephen Fesik, Ph.D.: "My interest is to develop therapies that will have a dramatic effect on cancer patients. Not simply trying to change a drug that is currently given twice a day to once a day, or to eliminate a slight side effect … I'm looking for the cures. Not the extension of one month or two months, but actual cures."

New class of cancer drugs

A team of Vanderbilt University Medical Center investigators has developed a group of chemical compounds that could represent a new class of drugs for treating cancer.

The compounds are the first selective inhibitors of the protein phospholipase D (PLD), an enzyme that has been implicated in multiple human cancers including breast, renal, gastric and colorectal.

The new inhibitors, reported in the February issue of *Nature Chemical Biology*, block the invasive migration of breast cancer cells, supporting their further development as antimetastatic agents. They will also be useful tools for understanding the complex roles of PLD in cellular physiology

The team – led by H. Alex Brown, Ph.D., professor of Pharmacology and Craig Lindsley, Ph.D., associate professor of Pharmacology and Chemistry – developed and screened compounds for activity against PLD1 and PLD2, two isoforms of the enzyme. They demonstrated that the compounds act directly on the PLD enzymes (using purified proteins).

Using a cell migration assay developed in the lab of Carlos Arteaga, M.D., director of the Vanderbilt-Ingram Breast Cancer SPORE (Specialized Program of Research Excellence), they were able to show that the inhibitors blocked the invasive migration behavior of three different breast cancer cell lines.

"These inhibitors are the key tools we need to really probe the biology, and we're obviously hoping to develop them for therapeutic applications too," Brown said.

The researchers will now optimize their new compounds for *in vivo* studies and to give them characteristics compatible with being good medications. In addition to studying the inhibitors in breast cancer models, they will also explore how they work in cell systems that model brain tumors, rheumatoid arthritis and viral infections.

– by Leigh MacMillan

web link
To read more about the research, go to:
www.vicc.org/news/?p=354

proteins that Fesik worked on previously at Abbott.

"We believe that by eliminating this chaperone – and we're hoping to do that with drug-like molecules – that the cancer cells will become sensitive to compounds like the Bcl2 antagonist (drug developed at Abbott)," says Marnett, who also directs the A. B. Hancock Jr. laboratories, Vanderbilt's first cancer research lab founded in 1972.

Industrious in academia

But why would researchers at an academic institution be able to accomplish what industry has not been able to?

Because, Fesik says, Vanderbilt has assembled the infrastructure – including strong centers in structural biology, chemical biology, imaging and proteomics – to go after these high-risk, undruggable targets.

"At Vanderbilt, I can carry these studies out and do things that might be against the 'dogma' about what's doable and not doable. It's a great environment to do high quality, innovative science and, in particular, cancer drug discovery," he says.

"Even though (drugging these targets) might be technically challenging, if we get it, it will affect the lives of many patients."

The hope is to, in time, establish a formal cancer drug discovery program similar to Vanderbilt's Program in Drug Discovery in neuroscience. It may take time – and additional funding – to realize that dream.

But this is exactly what academia should be doing, says Marnett.

"In the area of drug discovery, (academia) should not try to replicate what's going on in industry – because the resources are just so totally different – but we should be looking at projects that are very high risk and relatively low cost. We can take things up to a point, but it all comes down to resources."

Marnett predicts that Vanderbilt's cancer drug discovery efforts will show real results on fairly short order.

"I think we can definitely get drug candidates that work in animals. And once you've got something that works in an animal and have validated your target, that's a pretty valuable package (for a drug company to then license and continue developing)," he says.

With Fesik's focus on cancer drugs coupled with the existing research infrastructure at Vanderbilt, "we've now got all the tools in place," says Marnett.

"We will test new therapeutic hypotheses, and we'll definitely have molecules that will get as far as the clinic. I can't promise they're going to work in the clinic. But I'm very convinced that Vanderbilt has the strongest academic drug discovery program in the country."

Fesik agrees that the potential exists to make important advances in cancer drug discovery. That's why he chose to leave industry and come to Vanderbilt.

"What's driving me the most is the dramatic effects we may be able to have on the lives of cancer patients," Fesik says. "The only thing that can stop this is the lack of funding."

"We want to do risky things. The reason the pharmaceutical industry is successful from a monetary viewpoint is that they don't. They can still make money with less risk," Fesik explains. "But we're not a company. We have different goals. However, to succeed at reaching our goals we need additional funding from the outside."

Tailor-made drugs on the menu

Fesik's fragment-based drug design, which essentially "tailors" a drug compound to fit a target protein, goes hand-in-hand with the goal of personalized medicine, which "tailors" therapy to fit the particular genetic profile of an individual's cancer.

For decades, surgery, chemotherapy and radiation have been the gold standard treatments for cancer. But they are essentially "one-size-fits-all" treatments.

One of the most important advances in recent years has been the development of targeted therapies – drugs designed to kill only cells with particular molecular malfunctions as opposed to the less discriminating assault of traditional chemotherapy and radiation (which tend to kill all rapidly dividing cells).

These targeted drugs – like Iressa, Tarceva and Erbitux – have certainly helped some cancer patients live longer, but most targeted therapies only work in a small percentage of patients. And, when they do work, they seem to add only another few weeks to months of disease-free survival.

The disappointing results – again due to the fact that no two cancers are the same – highlight the importance of developing new anti-cancer drugs that will allow physicians more options in achieving truly personalized cancer care.

"Personalized medicine was a fantasy a few years ago because we didn't have much targeted therapy," Fesik says. "It didn't much matter whether you could determine what is driving the tumor if you have nothing to offer the patient that takes advantage of that knowledge."

Now that more and more targeted therapies are being developed – and hopefully several more that Fesik and colleagues will add to the list – personalized medicine seems within our reach.

Larry Marnett, Ph.D.: Academic centers should not only generate basic discoveries about cancer biology, "but then take that next step toward trying to use that information in a fashion that will benefit patients."

DEAN DIXON

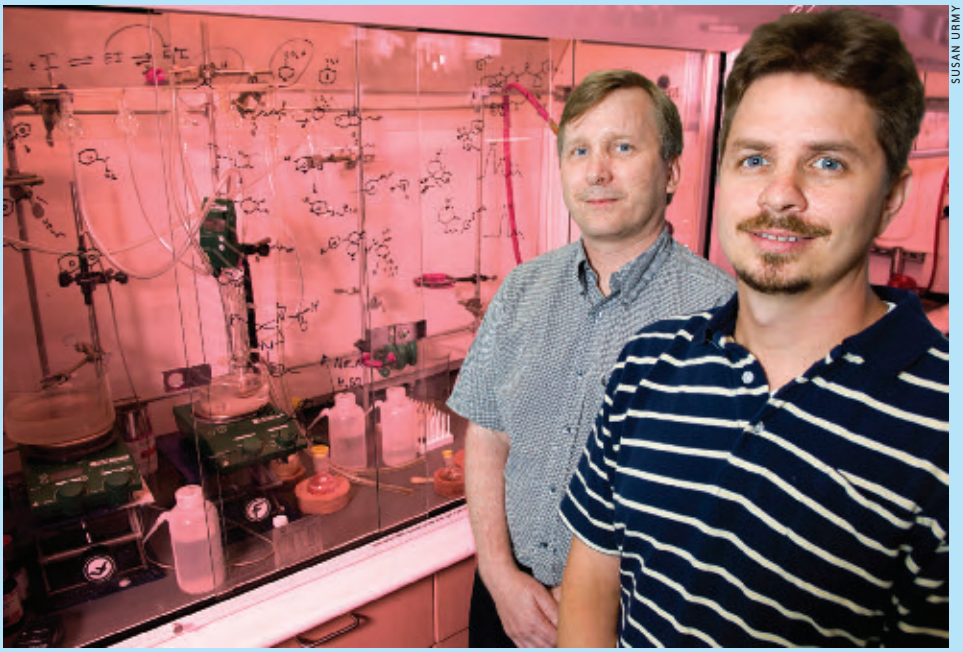
Larry Marnett, Ph.D.

"In the future, you could envision that you would diagnose the patient – not by tissue type but by the genetics – and then you would have this arsenal of weapons that you could use to treat the specific genetic malfunctions that are keeping the tumor alive," he says. "These are exciting times in cancer research as we get one step further to effectively treat cancer patients with new, innovative therapies."

web link

For more information about the Vanderbilt Institute of Chemical Biology, see: www.vanderbilt.edu/vicb

Vanderbilt joins effort to develop new cancer therapies



SUSAN URMY

Gary Sulikowski, Ph.D. (left) and Alex Waterson, Ph.D., are leading VUMC's efforts in the Chemical Biology Consortium.

Vanderbilt University was recently selected as one of 10 centers in the nation to participate in the Chemical Biology Consortium (CBC), a major new initiative to facilitate the discovery and development of new agents to treat cancer.

As one of four Chemical Diversity Centers, Vanderbilt's role in the consortium will be to synthesize and optimize new compounds as potential cancer therapeutics.

"This is a real tribute to our growth in cancer chemistry and the leverage between the Vanderbilt Institute of Chemical Biology and the Vanderbilt-Ingram Cancer Center," said Larry Marnett, Ph.D., the Mary Geddes Stahlman Professor of Cancer Research and director of the VICB.

Alex Waterson, Ph.D., research assistant professor of Pharmacology and director of the Chemical Synthesis Core of the Vanderbilt Institute of Chemical Biology (VICB), will lead efforts developing small molecule drug candidates. Gary Sulikowski, Ph.D., Stevenson Professor of Chemistry and a co-director of the core, will direct projects involving natural products.

Designed to accelerate the discovery and development of effective, first-in-class targeted therapies, the CBC will choose high-risk targets that are of low interest to the pharmaceutical industry. The CBC is a National Cancer Institute initiative administered by contractor SAIC-Frederick, Inc.

"It's exciting in the sense that, right off the bat, (the NCI) said that the goal of this program is to develop drugs for cancer treatment," said Sulikowski. "They're looking for unique targets, unique approaches, and they think that academia may offer that."

"Oftentimes pharmaceutical companies will not go after targets that are not expected to be huge blockbusters," said Waterson, who came to Vanderbilt in 2008 from GlaxoSmithKline where he had worked for seven years on oncology drug development projects.

"So an effort like this can fill in a niche that industry is not taking on at the moment."

One particular area of interest is in screening and developing natural products as potential drug candidates.

This "is something that pharmaceutical industry has de-emphasized just because of the way things have evolved," said Sulikowski. "And that's one of our advantages, in that we have expertise in natural products as well as medicinal chemistry."

Cancer drug development poses many challenges — but also unique opportunities.

"There is a difficulty in that cancer is not a single disease; it's a family of loosely related diseases," said Waterson. "There's an opportunity for a whole myriad of different treatments that are pretty much only tailored to a small subset of people, where your treatment addresses their specific need."

– by Melissa Marino

web link

To read more about the consortium, go to:
http://www.vicc.org/news/?p=789

You survived cancer. *Now* what?

By Dagny Stuart | Illustration by Nicholas Wilton

When Ron Obenauf turned 50, he decided to mark the milestone with a visit to his family physician for a physical and a colonoscopy. The CPA and real estate investor from Shelbyville, Tenn., received the physical, but when he asked about the colonoscopy, the doctor said he didn't recommend them until age 55.

"I told the doctor that my older brother had a colonoscopy and they found three precancerous polyps," Obenauf remembered. "My doctor turned around and said, 'I'll split the difference with you, and we'll do it when you turn 52 and a half.' I didn't push it anymore and in hindsight I should have."

A couple of months before

he turned 52, Obenauf noticed blood in his stool and immediately scheduled a colonoscopy with a local surgeon. The day after the procedure, the surgeon called and told Obenauf that he needed to talk to him right away.

"I asked if it was cancer, and he hesitated, then told me 'yes.'" By the time Obenauf heard the final diagnosis, his worst fear was confirmed. He had advanced colon cancer.

On that day in 2003, Ron Obenauf began his journey of survivorship, as one of the nearly 12 million cancer survivors in the United States. According to the American Cancer Society, the number of cancer survivors has tripled in the past 30 years and America's aging population will lead to even more cases of cancer in the future. A National Cancer Institute (NCI) study indicates that the number of cancer survivors in the United States will increase by 55 percent between 2005 and 2020.

However, support for those survivors has been slower to develop. Patients who end their cancer treatment often don't receive the information they will need for the rest of their lives. It's like being pushed out of the supportive hospital nest without being taught how to fly.

Ron Obenauf's journey, like that of other cancer survivors, has been full of physical and emotional shocks, setbacks and breakthroughs. No one said being a survivor would be easy.

"I was devastated and went through an emotional roller coaster ride for about 60 days," Obenauf said. "I was analyzing my entire life, the good and the bad and looking for blame."

It was just as difficult for his wife, Ardeth. "Ron has always been incredibly healthy, so to have something really major like this go wrong was like getting the rug pulled out from under us."

Within days, the cancerous section of Obenauf's colon had been surgically removed. Ardeth had been doing research, and the couple decided Ron should have the rest of his treatment at Vanderbilt-Ingram Cancer Center because of its NCI designation as a Comprehensive Cancer Center. His oncologist was Jordan Berlin, M.D., clinical director of Gastrointestinal Oncology at Vanderbilt-Ingram.

"Dr. Berlin told me my chance of long-term survival was 50-50, which wasn't very good odds," said Obenauf. "But he spent a lot of time with me explaining the pathology report and how many lymph nodes were involved and mapping out a treatment plan."

That treatment plan involved months of intensive chemotherapy. For more than a year, Ron appeared to be cancer free. But in January 2005, a lesion appeared in his liver, and he underwent more surgery to remove part of that organ.

That was the last time cancer appeared. Today, Ron gets regular checkups, which show no trace of a cancer recurrence, and he and Ardeth have added healthy food and exercise to their daily regimen.

"It's hard to describe, after what I've been through, how it feels to know that I'm here every day and I feel absolutely spectacular," said Obenauf. "There are a few lingering things that I'm probably going to deal with the rest of my life, like fatigue, but my life is good."

Still, when it's time for those regular checkups, Ardeth has episodes of anxiety – one of the hallmarks of life after cancer for survivors and their families.

"Being a cancer survivor is challenging," said Julie Means-Powell, M.D., an assistant professor of Medicine and breast cancer specialist at Vanderbilt-Ingram. "Even if their tumor was tiny, my patients tell me they are always waiting for the other shoe to drop. At any time in their life, while life is going really well, they are waiting for that cancer recurrence. So patients need to find ways to manage that stress and those of us in the medical community are finding better ways to support them."

Finding their way

The need for new and enhanced survivorship programs is clear. Amazing advances in childhood cancer treatments have created a new generation of adults who are cancer survivors. The NCI estimates that 14 percent of survivors were diagnosed 20 or more years ago.

Some treatment regimens are keeping patients alive years longer than before, creating a patient population for whom cancer is managed like a chronic disease.

JOE HOWELL

Ron Obenauf and his wife, Ardeth, charted their survivorship course after Ron's diagnosis of advanced colon cancer, making lifestyle changes as well as becoming involved in research and patient advocacy.

Whether they have been cured of their cancer or they are keeping the disease in check, patients have a range of physical, social and emotional challenges that need to be addressed by the medical community.

To help cancer patients and their families navigate life as a survivor, Vanderbilt-Ingram Cancer Center, the Department of Pediatrics and the Monroe Carell Jr. Children's Hospital at Vanderbilt have launched the REACH for Survivorship Program, a community resource to meet the unique needs of children and adults who have received a cancer diagnosis. Debra L. Friedman, M.D., is the director of the REACH for Survivorship Program.

"The goal of the survivorship clinic is to provide dedicated care focused on the survivor and not simply their cancer diagnosis," said Friedman, E. Bronson Ingram Chair in Pediatric Oncology. "We look at their medical needs with respect to both cancer and the effect of cancer treatment on other organ systems, as well as their psychosocial, functional and social needs."

The Survivorship Program – open to any patient regardless of where initial cancer treatment was received – is the only clinical program in the country that treats both adult and pediatric cancer survivors. The clinic is located outside of the Cancer Center, so survivors aren't thrust back into a hospital setting.

"We wanted the focus to be on wellness, not illness," Friedman explained.

The REACH for Survivorship Program recently added a second clinic at Nashville General Hospital at Meharry to serve even more patients.

Before patients ever walk in the door to one of the survivorship clinics, a multi-disciplinary team of health professionals reviews the patient's cancer and its treatment, health problems that may be related to the cancer, and issues of concern to the patient. This is accomplished through patient surveys and a careful review of medical records. A visit is then arranged. During the visit, patients meet with a social worker followed by a

The Survivorship Program – open to any patient regardless of where initial cancer treatment was received – is the only clinical program in the country that treats both adult and pediatric cancer survivors.

ANNE RAYNER

ANNE RAYNER

Deb Friedman, M.D., above, and Frances Niarhos, Ph.D.

physician or nurse practitioner who takes a detailed history of their cancer diagnosis and treatment and performs a thorough physical examination. Patients may be referred to other subspecialists, based on their treatment history, and they will be counseled about their medical risk factors and what they can do to keep themselves healthy.

Friedman says this kind of program is crucial because all too often a cancer patient leaves treatment without a roadmap for the rest of their life as a cancer survivor.

"Cancer survivors are at uniquely high risk for medical problems related to their initial cancer or the cancer treatment," said Friedman. "They need to be educated about those risks and what they and their doctors should look for and what special screening tests they may need throughout their lives. We put this all together in a coordinated package for them so they really understand what it means to adjust to a new normal."

That detailed individualized survivorship care plan, including a risk analysis, is sent to the patient's oncologist, primary care physician, specialists or any other care provider identified by the patient. The patient also leaves the survivorship session with a notebook filled with educational information, and a list of additional support resources.

Making the transition from cancer patient to long-term survivor can be stressful for patients and their families, especially when the patient is a child.

"From the time a child is diagnosed, the end of treatment is dangling in front of them like a brass ring," said Frances Niarhos, Ph.D., clinical psychologist in the Department of Pediatrics at the Monroe Carell Jr. Children's Hospital at Vanderbilt. "They don't realize that this transition time is going to be difficult, too."

Many children are at risk for neurocognitive late effects that are a direct result of the treatment they receive to fight the cancer. Cranial radiation for brain tumors may affect the way the brain grows and develops following treatment. Treatment for acute lymphoblastic leukemia (ALL) can also impact a child's development.

"Those children receive intrathecal chemotherapy, which is injected directly into the spinal column to target leukemia cells that remain hidden in the brain and cerebral spinal fluid," said Niarhos. "These intensive treatments may impact a child's neurocognitive development. It's not that they're not gaining skills following treatment, but they may not be gaining skills at the same rate as their healthy peers."

Niarhos and the other two psychologists on the survivorship staff recommend baseline neurocognitive testing for every child who has received treatment that places them at risk for late effects.

"The younger a child is when treated, the more likely that child is to demonstrate a late effects profile," said Niarhos. "For reasons we don't fully understand, girls seem more likely to develop neurocognitive late effects."

The psychologists work with teachers and school systems to help students succeed after cancer treatment.

"These are often bright kids but they may have very slow information processing speed," Niarhos explained. "It's not that they can't do the work their peers can do, but they need extra time in order to achieve at the same level. Once this is explained to the students, the parents and the schools, and they are given more time for things like standardized tests and other assignments, these students are able to flourish."

Hearts and Minds

Adult cancer survivors experience their own neurocognitive challenges. "Chemo brain" is the term survivors often use to describe the slow, fuzzy attempts to access memory and to process new information after treatment. This sluggish brain function can be frustrating and emotionally stressful to patients, especially adults who are trying to work during and after treatment. The REACH clinic is helping patients with these issues by providing referrals for support services.

Other long-term side effects of treatment are physical and they represent the double-edged sword that is cancer treatment. The very treatments that are supposed to save patients from cancer can put them at risk for other life-threatening diseases.

Some forms of chemotherapy, including anthracyclines, fall into that category.

"We treat some forms of breast cancer with anthracyclines, which puts those patients at risk for heart failure," said Julie Means-Powell. "The average cardiac risk for a woman at the dose we typically give is 2 to 4 percent. But women over age 65 or those who have longstanding hypertension are at increased risk. So there is definitely a chance that you could be cured of a cancer but then die from complications of heart failure."

Vanderbilt-Ingram oncologists are collaborating with physicians at the Vanderbilt Heart and Vascular Institute to monitor those patients. This cardio-oncology program is tightly coordinated with the REACH for Survivorship Program, and Friedman works closely with the cardiologists to develop pathways and studies for follow-up.

"They have helped me follow these patients with an integrated program, which I think is pretty unique," said Means-Powell. "They also are enrolling breast cancer patients in clinical trials to look for early signs of decreasing heart function during chemotherapy."

Other types of anthracycline chemotherapy drugs, like doxorubicin (Adriamycin), also increase the risk for acute leukemia in about one-half of 1 percent of cancer patients, so physicians must weigh the benefits of the drug against the serious risk of another illness.

Radiation therapy presents another challenge – the risk of a secondary cancer that develops years later in a small number of patients.

That's what Sarah Conley's physicians worried about when she was diagnosed with non-Hodgkin lymphoma at age 23. The young woman from Mansfield, Texas, had a family history of cancer – both of her parents are Hodgkin's lymphoma survivors.

"My doctors wanted to avoid radiation therapy because it increases the chance of breast cancer in young adults," said Conley. "So we did six rounds of chemotherapy and decided we would do more chemotherapy, if necessary."

Conley feels comfortable with the treatment plan.

"This is the primary cancer in young adults, and it's one of the more curable cancers," Conley explained. "After the first or second treatment, we did an X-ray and the tumor was already shrinking, so that was encouraging."

A year after treatment, Conley's cancer has not reappeared, and she is pursuing her dream career. She recently opened a voice studio in Dallas, Texas, teaching private voice lessons. She also founded a nonprofit organization, "How You Live," to educate young adults about the importance of having a primary care physician and obtaining health insurance.

"I hear about young people in their early 20s who were diagnosed with cancer or another serious illness while they were uninsured or had a lapse in their insurance," Conley said. "It creates a nightmare, causing a young person to be diagnosed late, which significantly decreases their chance of survival."

Conley believes it is a gift to have this opportunity to help other young adults and calls being a cancer survivor "an honor."

"I believe that survivorship begins the day you are diagnosed, and every day that you live with your disease, you are surviving," Conley said. "I feel privileged to be a part of that group of people that has an appreciation for life that others may not have, or perhaps we simply have a different perspective."

When she returns to Vanderbilt-Ingram for her next checkup, Conley plans to take advantage of the REACH for Survivorship program.

"My oncologist has kind of become my primary care physician, but I want my next physician to know about the long-term side effects I may face. Ten years from now, if I developed a problem, I would have something substantial to show to my doctors, and I would know more about what to expect."

Moving Forward

Back in Tennessee, Ron and Ardeth Obenauf have charted a clear path to survivorship. During Ron's treatment, they garnered much of their support from members of their small, close-knit church.

"My faith played a huge role in my survivorship," explained Ron. "I go to God in prayer and thanksgiving that I have been able to survive this disease."

FILE PHOTO

ANNE RAYNER

Sarah Conley with Vanderbilt nurse Connie Crawford-Koonce, R.N., during her treatment in 2007 (left), and today (right). Sarah is using her experience as a cancer survivor to help educate young adults about health care issues.

"I believe that survivorship begins the day you are diagnosed, and every day that you live with your disease, you are surviving."

While they did not join a formal support group during Ron's treatment, they helped set up a Web site called CanConnect (www.canconnect.org), an online support resource for Middle Tennessee cancer patients. They also decided to become research advocates as part of the Patient Advocacy Program at Vanderbilt-Ingram. Both work with colon cancer researchers, representing the patient perspective as investigators design and implement clinical trials.

"The doors have really been opened to us at Vanderbilt," explained Ron. "We are in meetings that are incredible, with the top scientists in the country – people like Dr. Hal Moses, Dr. Lynn Matrisian and Dr. Robert Coffey. These are huge names in cancer research and we are welcomed into the meetings."

Ron also serves as a patient research advocate for the Vanderbilt Tumor Microenvironment Network and the couple participates in the Tennessee Colorectal Polyp Study, investigating nutrition, the benefits of exercise, tobacco cessation and other healthy lifestyle initiatives.

"We were given the opportunity to help, and most people who aren't scientists are never given this option," said Ardeth. "It is a golden opportunity, and we have done what we could."

Ron and Ardeth decided to support the Vanderbilt-Ingram cancer research programs with annual financial gifts, and they also donate funds to the Monroe Carell Jr. Children's Hospital at Vanderbilt.

"We have been really blessed, and we live a wonderful life," explained Ardeth. "We realized it was a good thing for us to help other causes, places we thought could use a boost here and there. We fund research through Dr. Berlin, and at the end of the year, we get a report on the project and how the money was used. It has been gratifying for us to know what has been done with our money and what the results are."

The Obenaufs, along with other cancer patients and their families, have discovered that survivorship is a complicated and often rewarding journey. Ardeth describes it succinctly.

"Vanderbilt is helping us and others like us get our lives back on track."

web link

For more information about the REACH for Survivorship Program, see: www.vicc.org/cancersurvivor

Art of Survival

There are few experiences in life that evoke stronger emotions than a diagnosis of cancer. For patients, family members, friends and caregivers, living with cancer can evoke feelings of sadness, fear, anger, anxiety or helplessness. Alternatively, the diagnosis may spur patients and families to new levels of determination, resolve and freedom to embrace new challenges.

To express those deep emotions some members of the cancer community turn to art, creating beautiful and often poignant words, images, sculpture or music. Vanderbilt's new REACH for Survivorship Clinic is providing an outlet for those creative urges by holding writing workshops and displaying some of the artwork designed by cancer patients and family members.

"We display wonderful art here at Vanderbilt University Medical Center because we want the aesthetic to be beautiful for our patients and visitors," said Donna Glassford, executive director of Cultural Enrichment. "We also understand that the process of creating art can be therapeutic for patients and their families, helping them find a way to express complex emotions."

Recent research reveals that participating in visual arts activities can decrease symptoms of distress, anxiety and depression and increase psychological strength among patients and caregivers.

Several pieces of art currently on display in the Survivorship Clinic were created by cancer patients or their loved ones.

"We want the Survivorship Clinic to be a warm welcoming space full of reminders of encouragement," said Anne Washburn, M.P.H., associate director of the Office of Patient and Community Education. "Our survivorship program focuses on more than the disease. We provide a holistic approach to care and we want to encourage our families to express themselves artistically."

The clinic is filled with art created in several mediums. Hanging in the lobby are lovely pastel landscapes from artist Henry Isaacs, whose first wife died from breast cancer.

A striking wooden sculpture of a woman prominently displayed in the lobby was carved by Louise Calvin. The breast cancer survivor started carving in her 40s after a mastectomy and continued to create stunning artwork until her death at age 84.

Head and neck cancer patient Maurice Mantus donated an evocative black and white photo of an arched bridge reflected in a water of a stream below. He titled the image "Water Under the Bridge."

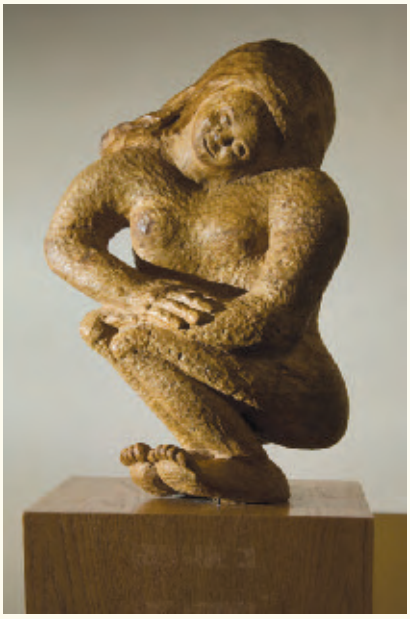
The process of creating art is clearly cathartic for patients and their loved ones. Artist Andi Seals, who plans to share some of her paintings with the clinic, is the widow of country music artist Dan Seals, whose early career was as one-half of the musical duo England Dan and John Ford Coley.

"Creating visual art does for me what singing, writing lyrics and music did for Danny," said Andi Seals. "It expressed his view of both the inner and outer world. When he was diagnosed with mantle cell lymphoma my painting style transformed. It switched without my conscious intention from representational realism to abstraction. It became a vital link between the experience of powerful circumstance and the processing of feelings that swelled up inside the soul."

Washburn said the pieces on display elicit positive emotions.

"Even when artists have passed away, their art represents hope."

– by Dagny Stuart



From top:

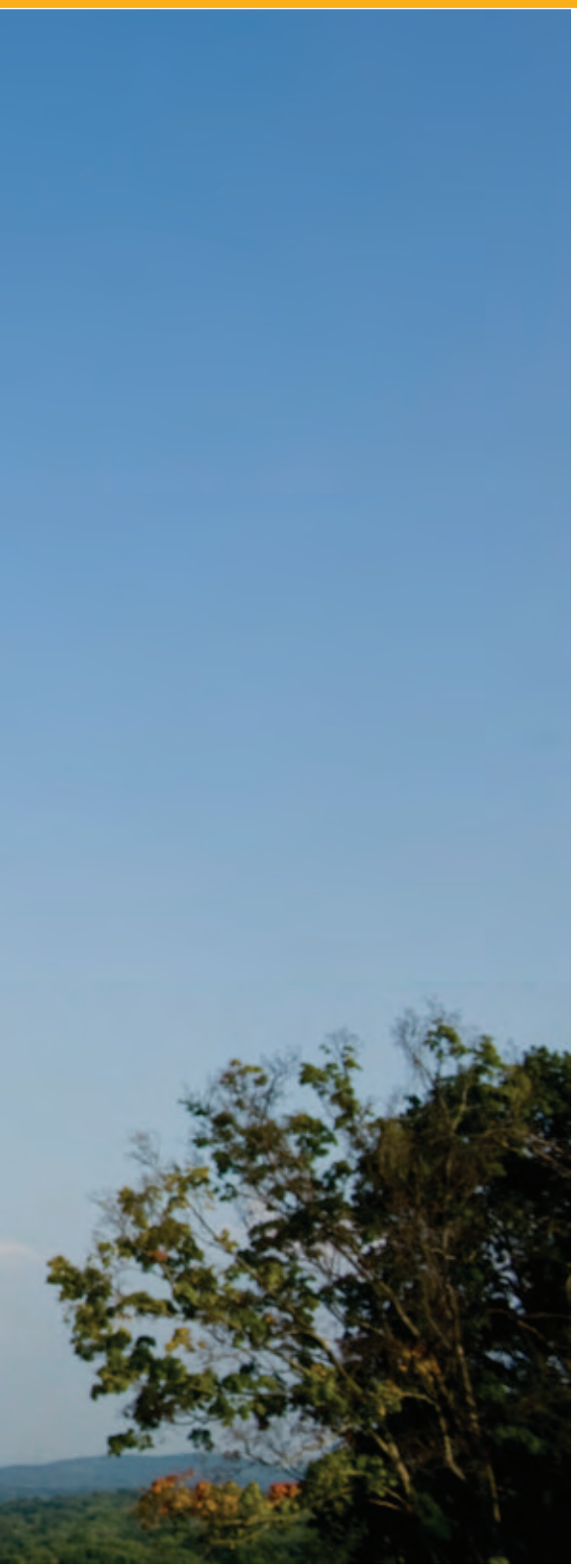
Pastel by Henry Isaacs, whose first wife died of breast cancer

Wooden sculpture of a woman by Louise Calvin, breast cancer survivor

STORIESOFSURVIVAL

KEVIN PLOTT

In His Own Words



"In the middle of difficulty lies opportunity."

– Albert Einstein

If Albert was right, I've had my share of opportunity. I've experienced – and survived – cancer three times as well as open-heart surgery. All by the age of 41.

Briefly, my résumé includes Hodgkin's disease at 15, melanoma at 26, colon cancer at 39, and a heart valve replacement at 41. The opportunity lies in the experience and new attitude toward life that I've gained. I truly believe I am a better person because of these health issues.

If you are dealing with major health challenges, I hope this experience and insight helps you meet those challenges. I share my story here, and volunteer with The Hope Connection, a telephone support program at Vanderbilt-Ingram Cancer Center, to provide a survivor's insight into the experience of cancer and to support others on the emotional cancer roller coaster.

By Kevin Plott | Photograph by Joe Howell

(1 CANCER)

Opposite page, (Left to right): Kevin in 1977, age 16, with his first car; working on the 1954 Chevrolet helped him through his treatments for Hodgkin's lymphoma (photo by Delores Plott).

While on medical leave for colon cancer, a neighborhood dog named "Snowball" started coming around…and never left; when Kevin returned home after heart valve replacement, Snowball was there to greet him. (photo by Delores Plott).

Vanderbilt nurse Karen Runyon with Kevin in May 2001 during his recovery from heart surgery.

Hodgkin's what?

In the winter of 1976, a lump grew on the right side of my neck, next to my collarbone. I was in good physical shape, and night sweats and fatigue were unusual for a 15-year-old. Dad took me to see our family doctor, and I was admitted into the hospital for tests the next day. Hospital, me? This was my first experience in a hospital since I was born and at first it was kind of neat … yeah, at first.

Three days later, I was on my way to Ohio State University for evaluation. This was very stressful for Mom and Dad. We had no idea what was in store or that OSU was going to become my home for the next month.

There were so many tests, you'd have thought I was trying out for the space program. The diagnosis was Stage IIA Hodgkin's lymphoma, and treatment included a splenectomy, three rounds of chemotherapy (specifically MOPP, or Mustargen/nitrogen mustard, Onvocin, Procarbazine and Prednisone). Next came 30 days of radiation. I can't recall having any problems with the radiation, except for my skin feeling like paper and losing some hair. Then, another three rounds of MOPP. The MOPP was intense, creating short-term effects of nausea and shingles, and the long-term effects of permanent sterility. But the most important effect was letting me live to see another day.

The long-term effects of radiation didn't show up for a while. Unknown at the time, I was born with a bicuspid aortic heart valve (seen in about 2 percent of the population). Usually these valves are treated or replaced later in life but not as young as 41. Apparently, the radiation to my chest accelerated calcification of my valve. Dr. Davis Drinkwater, then at Vanderbilt, replaced it with a mechanical valve in 2001, and I'm still ticking (literally).

(2 CANCER)

Melanoma

All was well for a few years. I had started night school and was very active. Then in 1984, I had a melanoma removed from the right side of my neck. A year later, the lymph nodes on the left side of my neck began to swell. Biopsies revealed mycobacterial infection, specifically Mycobacterium fortuitum (easy for them to say). The nodes would pop up weekly, and I would go have them biopsied … all infected with the bacteria. This went on for several months, and I was treated with antibiotics.

Then a lymph node on the right side of my neck swelled. I called my oncologist (Dr. Bertha Bouroncle at OSU) and explained I had another one, but this time it was on the right side. There was a moment of silence, and then she asked, "The right side? You should not be having a problem on the right side. Get down here to see me right now."

I was in for a biopsy of the swollen lymph node as soon as I arrived. The pathology results came back. Melanoma had invaded my lymphatic system. I was admitted that night.

Within a week, my tonsils were removed (not fun at 26), along with muscle, tissue and 37 lymph nodes in a radical neck resection. Half my neck was gone, but luckily all removed nodes were clean. Had I not been watched so closely, who knows how far the melanoma could have spread!

I had a tough time adjusting to the incision. For months, I ached from neck to shoulder. I couldn't turn my head and had difficulty moving my right arm. I've spent much of my life since being self conscious of the void in my neck. People often notice something is not quite right, but few inquire. I love it when someone is interested enough to ask.

I've learned to take life as it comes. The universe isn't out to get Kevin Plott, and I'm not being punished or suffering the effects of a karmic agenda. On the contrary, I believe I'm still around to share what I've learned and to help others dealing with cancer.

(3 CANCER)

Colon

Again, all was well for a few years. I was a healthy and active as ever. So much so, I grew a little complacent about my health. I was approaching 39 and had yet to have a colonoscopy. I knew of Dad's personal and family history with colon cancer, but for some reason it just didn't register. Boy, did I screw up.

In November 1999, I did (well, tried) a local 5K run with a friend. The gun went off, and I was huffing and puffing within a quarter mile. Then, a sharp pain in the middle of my back felt as if someone was driving a knee right between my shoulder blades. When I started experiencing tunnel vision, I stopped. That wasn't "out of shape." Something was wrong.

(I have a confession: these symptoms really began in September and here it was late November. I learned a big lesson here: never ever ignore your body. If something isn't quite right, get it checked out. Time to detect and treat a problem can mean everything – the difference between life and death, but also the difference between an easier and quicker treatment experience vs. pure hell with reduced chances of survival.)

My family doctor detected a heart murmur, so he referred me to a cardiologist. This was when I found out about my heart valve. I was crushed. Not again. Heart surgery? You have got to be kidding me! Little did I know that my heart valve was the least of my worries. Pre-op tests found me to be anemic. I was losing blood somewhere. A colonoscopy revealed a lemon-sized tumor in my transverse colon. The scary part was not knowing if it had gone through the colon wall and into other organs. Only surgery would tell.

Then came the realization:

"Any history of colon cancer in your family?"

"Uh, yes. My dad in 1988."

Then I thought, "who HASN'T had colon cancer?" That disease has devastated the Plott family. My grandfather, three uncles, two half-uncles and a half-aunt have all had it – and most have died from it.

Then my cardiologist arrives.

"You have us in a difficult position here."

Kevin promised himself this "dream bike" for making it through heart surgery. "I've been riding a bike all my life…I felt, as long as I can ride, I'm OK," he says.

JOE HOWELL

(*They're* in a difficult position?)

The challenge was to fix the artery before colon surgery. A coronary artery was discovered to be 80 percent blocked. To open it, they would insert a stent, requiring a platelet-inhibitor until tissue could grow over it. I would be on the drug right up to the colon surgery. Controlling the bleeding would be tricky.

Surgery confirmed my colon cancer at stage IIIB; the tumor had broken through the colon wall and into surrounding lymph nodes, but other organs were clear. However, I kept bleeding inside. I would get a unit of blood, pep up for a while, and then back down again. I went through 13 units of blood between my surgery on Wednesday and Friday morning.

I was going downhill fast and back on a gurney headed into surgery. This was the only time I doubted I would make it.

The anesthesiologist said, "You'll be out in a few sec…"

Then next thing I know, I'm waking up in post-op. I'm alive!

Surgery went well. I promised my parents and myself that I would do whatever it takes to make sure this turns out right. It was nice to finally leave ICU and get a regular room. Each day got a little better, and then pneumonia set in. But after what I had just been through, pneumonia? No problem.

I was released from the hospital on New Year's Eve. I settled myself on the couch and watched the millennium New Year's celebrations on TV.

I knew chemotherapy was in store – but not today.

I researched chemotherapy options and met with Dr. Jordan Berlin at Vanderbilt. We began 5-FU, but there were still unknowns. My blood counts were still low. I could be suffering long-term effects from my past chemo and radiation, and now we were putting more chemicals into my body. If my blood counts dropped much lower, I might have to stop … and stopping wasn't an option if I wanted to survive. Luckily, I tolerated the chemo.

A month after my last treatment, I completed an MS150 Bike Tour event – that's 150 miles on a bicycle, and it felt great.

(today)

Cancer-free

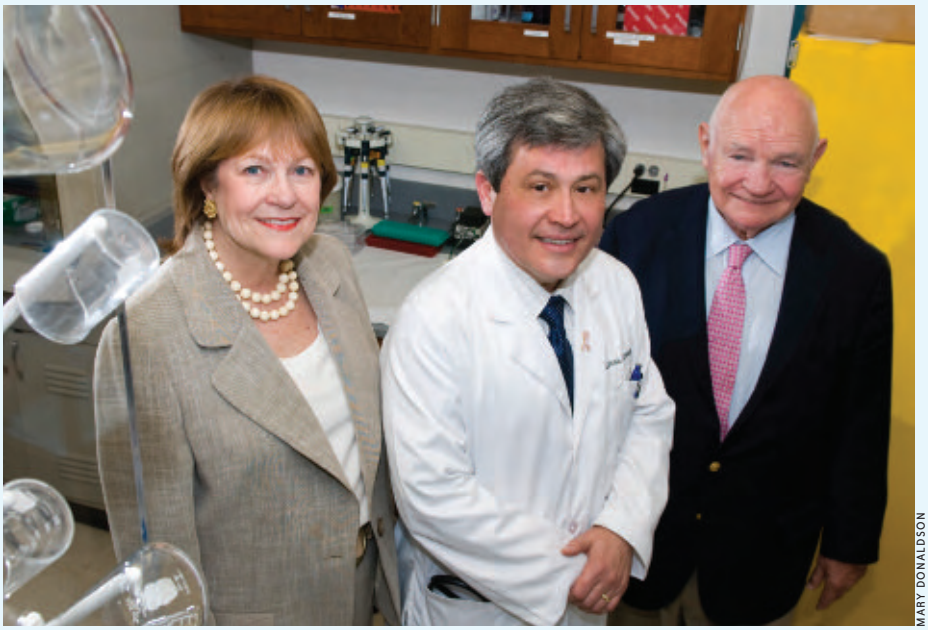
This year, I am celebrating 10 years cancer free. This milestone has inspired me to reflect on my experiences and realize just how fortunate I am. Fortunate not only to be alive to tell about it, but to have the opportunity to meet fellow "travelers" through my volunteering with The Hope Connection.

It's taken three bouts of cancer and 48 years, but I finally "get it."

I've learned to take life as it comes. The universe isn't out to get Kevin Plott, and I'm not being punished or suffering the effects of a karmic agenda. On the contrary, I believe I'm still around to share what I've learned and to help others dealing with cancer.

If I had a child, I would probably share these insights about living: Attitude is everything. Follow your heart. Don't take things personally or yourself too seriously. Always look forward. Listen. Laugh.

Oh, and ride your bike.



MARY DONALDSON

Donna S. Hall, Carlos L. Arteaga, M.D., and John Hall in the Arteaga laboratory at VICC.

"Dream Team" and new chair for Arteaga

Carlos Arteaga, M.D., professor of Medicine and Cancer Biology and director of the Breast Cancer Program at Vanderbilt-Ingram Cancer Center, has been named to one of the international cancer research "Dream Teams" funded by Stand Up To Cancer (SU2C), a charitable initiative of the Entertainment Industry Foundation designed to accelerate the pace of research to deliver new cancer treatments to patients.

Arteaga – along with VICC patient advocate and breast cancer survivor Patricia Lee – will be a part of a Dream Team initiative to discover approaches that will predict patients with breast, ovarian and uterine cancer who will respond to inhibitors of the PI3K pathway, which is mutated or abnormally activated in several human neoplasias. This work could help accelerate drug approvals and ultimately provide tests for personalized cancer treatment that can be incorporated into the standard of care.

Arteaga, director of the VICC Specialized Program of Research Excellence (SPORE) in breast cancer, is one of six principal investigators named to this Dream Team, which will receive a $15 million grant to support the three-year research program.

"I am thrilled our Breast Cancer Research Program is part of this multi-institutional and multi-disciplinary effort, as it will allow us to be at the forefront and contribute to this exciting area of translational research," Arteaga said.

Arteaga was also recently named the first recipient of the Donna S. Hall Chair in Breast Cancer at VICC.

The newly created chair – created to support the research efforts of an exceptional cancer investigator in the VICC breast cancer program – is funded through a $1.5 million gift from John and Donna Hall of Lexington, Ky.

The newly endowed chair will advance Arteaga's research on the pathogenesis and molecular therapeutics of breast cancer. His work helped pave the way for development of numerous targeted drugs such as trastuzumab (Herceptin), cetuximab (Erbitux) and erlotinib (Tarceva), as well as other combinations currently in development.

"It is a wonderful privilege to be awarded this new chair," said Arteaga. "John and Donna Hall have been steadfast supporters of the Cancer Center and this gift is another example of their commitment to research that may enhance the lives of cancer patients."

– by Dagny Stuart

Increasing African-American participation in clinical trials

While African-Americans are more likely to be diagnosed with certain forms of cancer and are far more likely to die of the disease, they also are less likely to enroll in cancer clinical trials, accounting for just 2.5 percent of participants nationwide.

At the 2009 American Association for Cancer Research (AACR) conference in Denver, investigators from Vanderbilt-Ingram Cancer Center and Meharry Medical College reported the completion of a multi-year recruitment trial in which 68 percent of those minority patients eligible for a cancer clinical trial agreed to participate.

In 2000, VICC and Meharry investigators established a clinical trial shared resource at Nashville General Hospital at Meharry. Most of the patients at this facility are uninsured or underinsured, and 55 percent are African-Americans.

"We discovered that these minority patients were just as interested in clinical trials, but they were more likely to have logistical barriers that made enrollment difficult," said Debra Wujcik, Ph.D., R.N., lead author and director of Clinical Trials at Meharry.

Those barriers – including missed appointments, lack of transportation, inadequate insurance, miscommunication and lack of patient understanding – were identified during the first year of the study and program procedures were adjusted during succeeding years to address them.

Since 2001, 1,125 patients have been screened, 343 (30 percent) had a study available, and 233 (21 percent) have enrolled. Overall, 68 percent of those eligible for a study agreed to participate.

"Clinical trials are discussed with the patient during the first conversation about treatment," said Wujcik.

"The trial is not offered as an afterthought and patients do not have to go to another center. They can participate in a trial in their own cancer center and be cared for by the staff and doctor they know."

– by Dagny Stuart

New radiosurgery, infusion services for VICC patients

Vanderbilt-Ingram Cancer Center has opened a new radiation oncology suite that features stereotactic radiosurgery, a technology that provides more precise targeting of tumors and faster delivery of the correct dose of radiation for patients diagnosed with benign or malignant tumors.

VICC's new Novalis Tx radiosurgery unit is the first of its kind in Middle Tennessee.

"Here at Vanderbilt we are at the forefront of delivering stereotactic, or more focused, radiation," said Arnold Malcolm, M.D., interim chair of the Department of Radiation Oncology. "We also are looking at hypofractionated radiation, which means giving a curative dose in a shorter period of time without damaging normal tissues."

The new radiosurgery system, developed by Varian Medical Systems and BrainLAB, has several advantages over existing technology, said Malcolm.

The delivery of radiation is so precise it can target tissue less than a millimeter in size - about the thickness of a fingernail. The new technology also delivers an accelerated radiation dose much faster than before and reduces required beam-on time by half.

"This leading edge technology is a major breakthrough and allows neurosurgeons and radiation oncologists the ability to precisely and non-invasively guide a narrow beam of radiation directly to the tumor," said Reid Thompson, M.D., professor and vice chair of the Department of Neurosurgery. "We can safely treat patients with surgical precision without an incision."

Cancer patients now also have expanded access to chemotherapy services at Vanderbilt-Ingram. In May, the VICC Chemotherapy Infusion Clinic moved into renovated space in The Vanderbilt Clinic.

The new clinic – financed through University funding and the support of VICC donors – provides more space, with nearly twice the number of chemotherapy chairs. Additional patient rooms will shorten the length of time patients wait before being placed in a room.

Other improvements include: more comfortable and user-friendly chairs, flat screen TVs with built-in DVD players in each room, a larger waiting area and a family break/vending room, a full wig fitting room, and an area for volunteers to work with patients and their families.

Staff members are also benefitting from the design of the new facility. Updated equipment and larger spaces will allow the staff to be more efficient in providing care to patients.

– by Dagny Stuart

Left: Idiko Csiki, M.D., Fen Xia, M.D., Ph.D., and Tony Cmelak, M.D., (left to right) examine the new radiosurgery technology.

Below: The new Chemotherapy Infusion Clinic houses 23 treatment rooms and 45 treatment chairs.

SUSAN URMY

SUSAN URMY

Zheng's cancer research lands MERIT Award

Vanderbilt cancer epidemiologist Wei Zheng, M.D., Ph.D., M.P.H., has received a MERIT Award from the National Institutes of Health (NIH) for his research on women and cancer.

The MERIT (Method to Extend Research in Time) awards provide long-term support to investigators with impressive records of scientific achievement in research areas of special importance or promise. Fewer than 5 percent of NIH-funded investigators are selected to receive MERIT awards, which provide financial support for up to 10 years without competitive review.

Zheng's MERIT award will support continuation of the Shanghai Women's Health Study, a population-based study of 75,000 women who were recruited between 1997 and 2000 with a major focus to identify associations between diet and lifestyle and diseases such as cancer.

Zheng and his team are studying the impact of soy foods, tea, ginseng and cruciferous vegetables on cancer risk and health. The researchers also are conducting genome-wide association studies, scanning the entire genome for disease susceptibility biomarkers. They are studying telomeres, DNA copy number variations, prostaglandin metabolites and other biomarkers that may be important in cancer and other disease processes.

"One of our goals is to build a risk-assessment model for breast cancer that will allow us to identify those women at high risk for the disease for cost-effective prevention," said Zheng, Ingram Professor of Cancer Research and director of the Vanderbilt Epidemiology Center.

"I am very excited to receive this award. It is a recognition of the teamwork involved in our research," he said. "Epidemiological studies require a multidisciplinary team, and I am privileged to work with so many talented, dedicated people at Vanderbilt and many other institutions."

– by Dagny Stuart

SUSAN URMY

JoGale Ray is a volunteer with the new Hope Connection telephone support program for cancer patients.

Support program connects cancer patients, survivors

Coping with a cancer diagnosis can be a scary and emotional ordeal. Time spent in doctors' offices, chemotherapy chairs and radiation suites often reinforces feelings of loneliness for cancer patients and their families.

So Vanderbilt-Ingram Cancer Center has launched the Hope Connection, a free confidential support program for adult cancer patients and their families. The Hope Connection provides one-to-one telephone support from caring, compassionate volunteers who have personally experienced the challenges and complex issues of a cancer diagnosis. The volunteers are cancer survivors and caregivers who are willing to listen, provide guidance and offer support before, during and after cancer treatment.

"Patients and their families have been telling us that they need more emotional and personal support as they move through the cancer journey," said Jane Kennedy, manager of Patient Advocacy for Vanderbilt-Ingram. "At the same time, many survivors and caregivers want to help someone else going through this experience. By providing encouragement, guidance and coping strategies, the volunteers help individuals reduce their fear and uncertainty."

To date, 24 Hope Connection volunteers have been trained to provide telephone support to any patient or family member who wants to connect with someone who has been there. Individuals are matched with volunteers who have experience with the same type of cancer or medical issue.

Volunteers must be 18 or older and at least one year past treatment. They are asked to make a minimum one-year commitment to the program. Volunteers will undergo a criminal background check and must complete training to prepare them for their peer support role.

The Hope Connection program does not take the place of the care and support patients get from their medical team. Volunteers help individuals reduce fears, strengthen their ability to cope, and feel more prepared for treatment and decision-making.

For more information, or referrals, please call (615) 936-8501, or e-mail jane.kennedy@vanderbilt.edu.

– by Dagny Stuart

web link

Visit www.vicc.org/hope for additional program or volunteer information.

Vanderbilt again makes U.S. News 'honor roll,' best in cancer

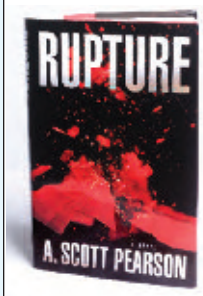
Vanderbilt-Ingram Cancer Center has been ranked as the 13th best cancer program in the United States by *U.S. News & World Report*, marking several years of top 20 rankings on the prestigious list of Best Hospitals.

Overall, Vanderbilt University Medical Center maintained its honor roll status for the second straight year by placing 16th in the nation in *U.S. News & World Report's* 2009-2010 publication of America's Best Hospitals, released July 17.

To be eligible for the honor roll an institution is required to have high rankings in at least six specialties. Nine VUMC specialty programs ranked among the top 50 in their respective fields: Kidney (9), Urology (10), Cancer (13), Diabetes and Endocrine Disorders (15), Gynecology (16), Ear, Nose and Throat (16), Heart and Heart Surgery (17), Respiratory Disorders (18) and Digestive Disorders (32).

No other Tennessee hospital made the list in any category.

– by Craig Boerner



Medical mystery

A. Scott Pearson, M.D., associate professor of Surgery, recently published his first novel, "Rupture," a thriller set at a teaching hospital in Memphis. The title refers to the unfortunate – and criminal – simultaneous failures of implanted medical devices.

"Rupture" is available at local bookstores, including Davis-Kidd and Borders on West End, in Nashville, Tenn., and at online booksellers, including www.Amazon.com and www.rupturenovel.com.

web link

To read more about Pearson and his writing, see: www.mc.vanderbilt.edu/houseorgan

JOURNAL WATCH

Vanderbilt-Ingram Cancer Center is committed to conducting innovative, high-impact basic, translational and clinical research with the greatest potential for making a difference for cancer patients, today and in the future. Here's a sampling of recent work published in peer-reviewed journals by center investigators:

Cancer biomarker boost

Daniel Liebler, Ph.D., Lisa Zimmerman, Ph.D., and colleagues in the National Cancer Institute's Clinical Proteomic Technology Assessment for Cancer (CPTAC) program have developed a new method for detecting and quantifying cancer-associated proteins in body fluids. The new method combines two existing mass spectrometry-based technologies: multiple reaction monitoring (MRM) coupled with stable isotope dilution mass spectrometry (SID-MS). In the July issue of *Nature Biotechnology,* they report that this combination of proteomics methods increases accuracy and reproducibility of candidate biomarker verification, ensuring that the best biomarker candidates are carried through to clinical validation. The findings may offer a major boost to the development of biomarkers to aid in early cancer detection and personalized cancer therapy – including the development of blood tests for cancer detection.

Gene signature predicts breast cancer prognosis

Vanderbilt-Ingram researchers have uncovered a gene signature that may help predict clinical outcomes in certain types of breast cancer. In the June issue of the *Journal of Clinical Investigation,* Harold (Hal) Moses, M.D., and colleagues report that this gene signature – which is associated with the transforming growth factor-beta (TGF-β) signaling pathway – correlates with reduced relapse-free survival in patients with breast cancer, especially in those with estrogen receptor-positive tumors. The results suggest that assessing TGF-β signaling may be a useful aid in determining breast cancer prognosis and in guiding treatment. The work also sheds light on how TGF-β affects tumor growth and progression.

Breast cancer 'hot spot'

Wei Zheng, M.D., Ph.D., and colleagues have identified a new genetic hot spot for breast cancer on chromosome 6. Reported in the March issue of *Nature Genetics*, this genetic variation – a single nucleotide polymorphism (SNP) – may explain about 18 percent of breast cancer cases in the general population. Women with one copy of this SNP have about 40 percent increased risk of breast cancer; having two copies of the SNP increases risk about 60 percent. Although the function of the SNP is not clear, it is strongly associated with estrogen receptor (ER)-negative cases of breast cancer, which carry a worse prognosis than ER-positive cases. Zheng hopes to use this SNP and others to build a risk prediction model that could help identify high-risk women for chemoprevention or regular cancer screening to reduce their breast cancer mortality.

Sweet approach to cancer prevention

The main sweet-tasting chemical component of licorice (glycyrrhizic acid) may offer a new approach to preventing colorectal cancer without the adverse side effects of other preventive therapies. In a study published in the April *Journal of Clinical Investigation*, Raymond Harris, M.D., Ming-Zhi Zhang, M.D., and colleagues show that inhibiting the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) – either by treatment with glycyrrhizic acid or by silencing the 11βHSD2 gene – prevents colorectal cancer progression in mice predisposed to the disease. While this natural chemical is an appealing drug lead in itself, the researchers are working to develop more specific and potent inhibitors of 11βHSD2.

Life and death in the stomach lining

Infection with the gut bacterium *Helicobacter pylori* increases the risk of gastric cancer, in part by disrupting the delicate balance between cell proliferation and death in the stomach lining. Using gastric cell cultures and mouse models of *H. pylori* infection, Brent Polk, M.D., and colleagues found that the bacterially induced activation of the epidermal growth factor receptor (EGFR) – a molecule that regulates cell survival – protects gastric epithelial cells from programmed cell death (apoptosis) and that blocking this activation increased *H. pylori*-induced apoptosis. The findings reported in the April issue of *Gastroenterology* offer insights into how *H. pylori* infection might contribute to the development of gastric cancer and support the strategy of targeting EGFR for cancer prevention or treatment.

Lithium shields brain from radiation damage

Cranial irradiation is part of standard therapy for both primary and metastatic brain tumors. However, as with all treatment modalities, radiation often causes long-term side effects. In particular, neurological impairments – including lowered IQ, learning difficulties and memory loss – have been reported, especially in children treated for brain cancers. In the May issue of the *Journal of Clinical Investigation,* Fen Xia, M.D., Ph.D., and colleagues show that lithium – a drug widely used to treat bipolar mood disorder – promotes DNA repair in healthy cells but not in brain tumor cells. The findings suggest that lithium treatment could offer a way to protect healthy brain tissue from damage that may occur during cranial radiation treatments.

web link

More information about our research at:
www.vicc.org/research

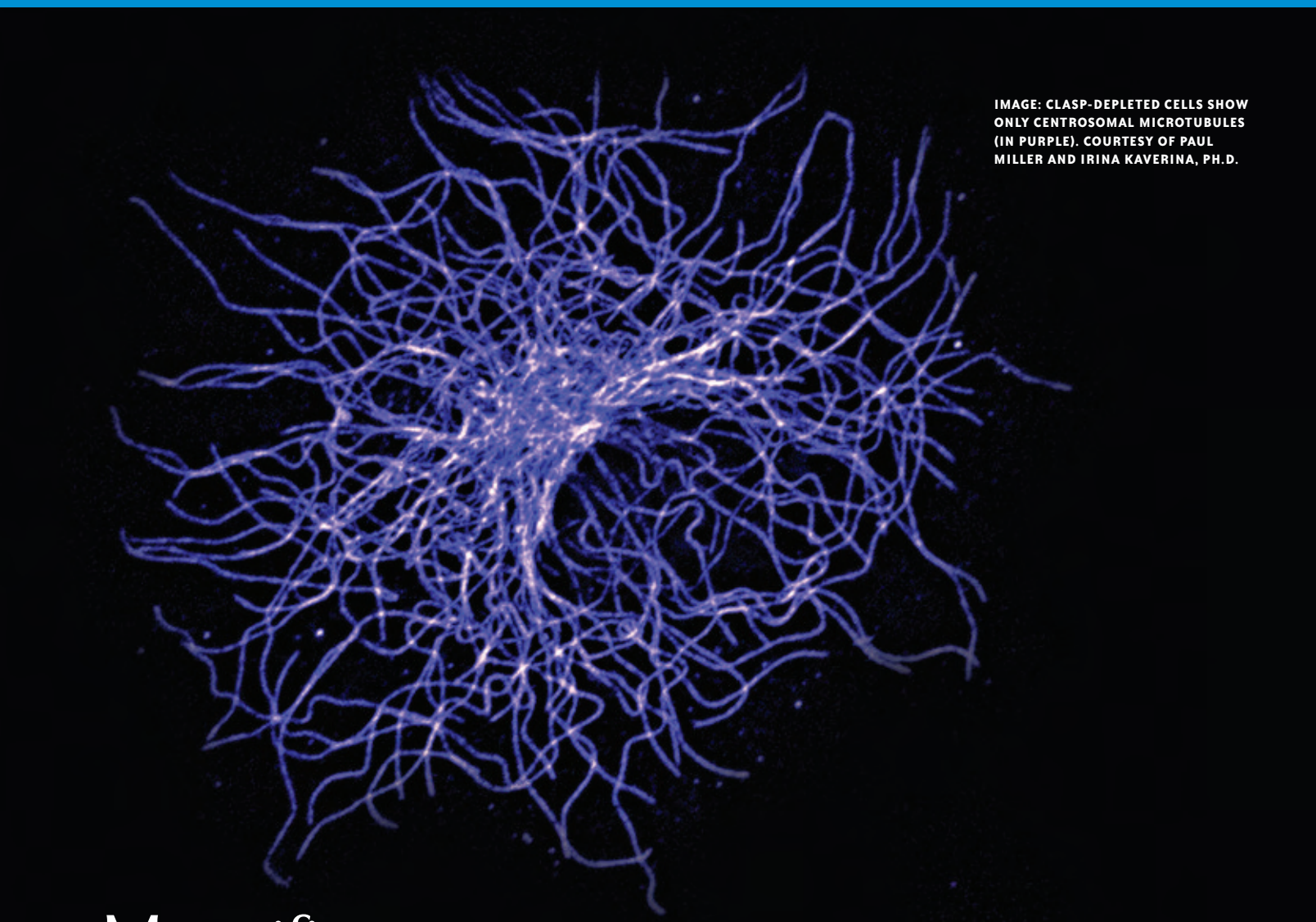


IMAGE: CLASP-DEPLETED CELLS SHOW ONLY CENTROSOMAL MICROTUBULES (IN PURPLE). COURTESY OF PAUL MILLER AND IRINA KAVERINA, PH.D.

Magnificent microtubules

Microtubules are a main component of the cell's internal scaffolding (cytoskeleton). These filaments help transport organelles and proteins throughout the cell, which is important for cell migration. Their role in cell movement is central to the ability of cancer cells to metastasize and invade healthy tissues.

VICC member Irina Kaverina, Ph.D., assistant professor of Cell and Developmental Biology, and colleagues are studying a particular set of microtubules that originate from the Golgi complex – a structure inside the cell that processes and packages proteins for transport.

Kaverina and colleagues have found that depleting cells of proteins known as CLASPs eliminates these Golgi-derived microtubules, leaving only microtubules that originate from the centrosome – the main source of microtubules in the cell. They are using this cell model system to study the function of Golgi-derived microtubules.

This research – for which Kaverina was awarded a 2009 Vanderbilt Chancellor's Award for Research and a VICC High Impact Research award in 2008 – may have important implications for cancer cell invasion and the actions of chemotherapy drugs. Their latest findings are published in the September issue of *Nature Cell Biology*.

momentum

VANDERBILT UNIVERSITY
VANDERBILT-INGRAM CANCER CENTER

Office of News and Public Affairs
D-3237A Medical Center North
Nashville, TN 37232-2390

NON-PROFIT ORG.
US POSTAGE
PAID
NASHVILLE, TN
PERMIT NO. 1446

Art of Survival

Art helps patients and their families express the emotions evoked by a cancer diagnosis.

page 31