

Moving toward a future without cancer.

momentum

08
spring

IN THIS ISSUE: FOUND IN TRANSLATION • NAVIGATING CANCER CARE • PULLING CANCER'S ROOTS



Cancer
Hot Spot

Where you live matters when it comes to cancer risk

On the cover:

States with the highest death rates from cancer “just light up” on the map. Researchers want to understand why ... and do something about it. See page 8.

Pictured below:

Brain cancer stem cells stained for the structural protein vimentin. An emerging area of research focuses on the notion that cancer stem cells may be the best target yet for treatment. Story begins on page 14.

Image by Steven Pollard/Wellcome Images

EDITOR & ASSOCIATE DIRECTOR, COMMUNICATIONS
Cynthia Floyd Manley

DESIGN & ART DIRECTION
Diana Duren

SENIOR EDITOR-IN-CHIEF
Nancy Humphrey

DIRECTOR OF PUBLICATIONS
Wayne Wood

CONTRIBUTING WRITERS
Dagney Stuart
Elizabeth Older
Leigh MacMillan
Melissa Marino
Pam Martin
Cynthia Floyd Manley

PHOTOGRAPHY/ILLUSTRATION
Neil Brake
Dean Dixon
Dominic Doyle
Dana Johnson
Anne Rayner
Tamara Reynolds
Nicholas Wilton

COVER ILLUSTRATION
Photo by Dean Dixon

EDITORIAL OFFICE
Vanderbilt-Ingram Cancer Center
2220 Pierce Avenue
691 Preston Research Building
Nashville, TN 37232-6838

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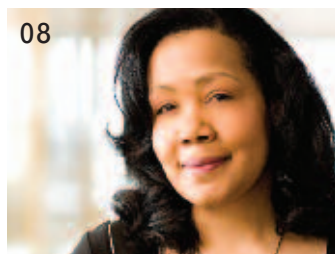
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Moving toward a future without cancer.

momentum

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To view Momentum online, log on to <http://www.vicc.org/momentum>



Director's letter

I am honored to present this issue of *Momentum* in a new role, as director of the Vanderbilt-Ingram Cancer Center. The name of this publication is so appropriate, because we have reached a point of tremendous momentum against this set of diseases called cancer. The decline in the overall cancer death rate in the United States continues in large part because the investment in cancer research in past decades is beginning to pay a return.

However, we still have a lot to do. Tennessee is one of seven contiguous states with the highest cancer death rates in the nation. Vanderbilt-Ingram Cancer Center is located at the very buckle of this "Cancer Belt." We are one of only two Comprehensive Cancer Centers in these states, and as such, it is our obligation to focus our work where we can make the most impact. Until those outcomes change significantly, our jobs are not done.

I am excited about my new role because I am confident that this team of talented researchers, physician-scientists, and other professionals at Vanderbilt-Ingram can make a difference. I consider it an incredible privilege to bring together their strengths as we work together, and with colleagues locally and around the world, toward an important and compelling objective. Simply put, we want to eliminate death and suffering from cancer. We do this for our patients and families by delivering first-rate, evidence-based care in our clinic. We do this by

reaching out to our neighbors and helping them understand and take steps to reduce their cancer risks. We do this on a global scale through our innovative science and translational research.

I am pleased to report on some of the progress that we're making. In this issue of *Momentum*, you'll see how advances in cancer are "found in translation" through the deliberate and focused process known as translational research. You'll learn about new frontiers in imaging and in stem cell biology that offer new insights about cancer treatment and prevention.

You'll read about work to understand why residents of the Southeast face

a greater risk of developing and dying from cancer than those who live in other parts of the country.

Most importantly, you'll meet people whose lives have been changed by cancer and who share their experiences in these pages: Ardythe Jones, a woman on a quest for answers about cancer of unknown primary, the mysterious and maddening cancer that claimed the life of her husband, Frank; Pam Martin, a breast cancer survivor who shares the lessons she learned along her cancer journey; Teresa Lundberg, the beneficiary of decades of research that began with a curious observation – that snake venom could make baby mice open their eyes sooner – and with no expectation that it had anything to do with cancer; and Jim and Brigitte Grant, whose decision to seek a second opinion made all the difference.

I hope that you enjoy this issue of *Momentum* and that its content will spark conversation and inspire you to learn more at our Web site, www.vicc.org. And because virtually everyone has been touched by cancer, directly or indirectly, please share this magazine with family, friends, co-workers or neighbors.

Jennifer Pietenpol

I am excited about my new role because I am confident that this team of talented researchers, physician-scientists, and other professionals at Vanderbilt-Ingram can make a difference.

ACLOSERLOOK

ANNA BELLE LEISERSON

Web Coordinator, Vanderbilt-Ingram Cancer Center



PHOTO BY NEIL BRAKE

WHEN VANDERBILT-INGRAM'S WEB COORDINATOR, ANNA BELLE LEISERSON, WAS trying to decide on a major in college she didn't go with her instincts. "I wanted to be a computer science major, but I had this thought run through my head that computers weren't for women." So she became a librarian instead and landed her first job as the librarian at a men's prison in Massachusetts.

Eventually Leiserson and her husband moved to Nashville where she became a law librarian for Vanderbilt University. That's when her first love reappeared. "When computers returned to my life, I latched on to them. And when the Web showed up I fell in love. The Web is such a natural for a geeky librarian – it's information at your fingertips."

Leiserson did more than just surf the Internet for interesting information. She devoured primers on computer programming and Web site design.

"Early on, Web programming was pretty simple, so it was easy to teach yourself just by reading books," explained Leiserson. She continued to hone her computer skills until she was ready to design her first Web portal, an international Web site for librarians. Since Leiserson's family moved around a great deal – she lived in England and Zimbabwe as a child – her international perspective proved invaluable for a Web site with global reach.

Officials with Vanderbilt Law School soon recognized her growing expertise and asked her to become their Webmaster. Nearly a decade later she moved across campus, bringing those Web design skills to the Vanderbilt-Ingram Cancer Center. Her first task was to revitalize the Web site, making it a more powerful tool for cancer patients and caregivers. Patients can now learn more about cancer research under way at Vanderbilt-Ingram, search for a physician in the "find a doctor" directory, find out how to become a patient, and get tips for cancer prevention. The site allows Vanderbilt-Ingram's renowned cancer researchers to reach out to patients and share information about clinical trials. The Web site also provides seamless links to other partner organizations like the National Cancer Institute, the National Comprehensive Cancer Network or the American Cancer Society.

"You have to be very holistic in your approach and consider more than just the look and feel of the site," explained Leiserson. "It's not just the programming, it's not just the content, it's not just the information architecture. You have to work with all of those pieces, tend to them and get them to play nicely."

Leiserson's attention to detail is evident on the revamped and expanded Web site, www.vicc.org, which rolled out in 2007 and now receives more than 17,000 unique visitors per month.

"Since Anna Belle took the reins of [vicc.org](http://www.vicc.org), our traffic has just about tripled," said Cynthia Manley, the center's associate director for communications. "Research shows that one of the first places patients and families go for information when they face a cancer diagnosis is the Internet, so we can't underestimate the Web site's importance."

Though not involved in direct patient care or research, Leiserson is motivated by the center's mission to heal. She recently learned that a woman in the country of Lebanon found one of Vanderbilt-Ingram's physicians through a simple Google search, traveled to Nashville for treatment, and is now a cancer survivor. "This job is wonderful because the mission is so meaningful. Just to work here is truly a privilege."

Leiserson is equally attuned to the world outside the cancer center. "My church is my passion," Leiserson said with a smile. "I love parenting my two daughters, and I love to cook." She shares those duties with Alan, her husband of 33 years and an attorney specializing in environmental law.

Leiserson dishes up her own insights on her church and work on the personal blog she recently launched. She also is one of the founders of the local "Ada Loveless Society," named after Lord Byron's daughter, the first known female computer scientist. "She was an amazing woman, helping Charles Babbage back in 1843 write about computing, and even visualizing things like digital music," Leiserson said.

Following in Ada Loveless's footsteps, Leiserson is making her own mark in the digital world – all because she decided that women could be computer experts, too. ☉

– by Dagny Stuart



Check out Anna Belle's blog at www.happywebdiva.com.



SPOTLIGHT: RARECANCER

FRANK AND ARDYTHE JONES

Cancer of unknown primary





a family's quest

Determination to find answers to mystifying cancer leads to Discovery Grant in husband's memory

Ardythe and Frank Jones were man and wife for more than 50 years. They enjoyed two children, four grandchildren, and life on the road in their RV, touring the country together.

They also both faced cancer less than a year apart, but their experiences were as different as night and day.

When Ardythe was diagnosed with breast cancer in 2005, she was presented with mountains of information, lists of resources, and perhaps most importantly, optimism and hope. When Frank learned he had cancer in 2006, there



was little information. Few resources. No hope.

“When we went back to our oncologist after Frank’s surgery, he said, ‘what I tell people in this situation is to get their financial affairs in

order,’” Ardythe recalls. “They automatically put you in a box for death and that’s the end of it.”

Why the difference?

The tumor growing around Frank’s spinal cord was diagnosed as “cancer of unknown primary,” or CUP. It had spread from an original (primary) tumor somewhere else in his body, a tumor that was never found or identified.

By Cynthia Floyd Manley | Photography by David Hills

PHOTO BY NEIL BRAKE



Gregory Mundy, M.D., is leading research into the specific biologic mechanisms that underlie the spread of tumor cells to bone. This is a significant complication of cancer of unknown primary. For many patients with this type of cancer, the greatest “tumor burden,” or total of cancer cells and tissue in the body, is found in bone.

The key to understanding CUP is to understand first how cancer often develops and spreads. Abnormal cells grow and cancer begins in one kind of tissue; this first tumor is called the “primary site.” One characteristic of cancer is that the cells have the ability to spread and begin to grow in other distant parts of the body (metastasis). These “metastases” are still the same type of cancer as the original tumor. For example, a cancer that starts as a breast tumor but spreads as tumors in the bones or brain is still a breast cancer, and is treated as such. Treatment that is specific to the type of cancer is likely to be most effective.

However, sometimes a tumor’s location and what it looks like under the microscope suggest that it began somewhere else. The pattern of spread, what the cancer looks like, a patient’s personal or family history, and other factors may offer clues to the tumor’s origin. The National Cancer Institute estimates that 2 percent to 4 percent of patients have a cancer for which the site of origin is never found. That adds up to as many as 56,000 of the 1.4 million Americans expected to be diagnosed with cancer in 2008. While dwarfed by the 213,000 who will develop lung cancer or the 180,000 who will develop breast cancer, it is similar to the number of patients who develop kidney cancer or melanoma – “still a lot of people,” Ardythe says.

The National Cancer Institute estimates that 2 percent to 4 percent of patients have a cancer for which the site of origin is never found.

Among those affected by this devastating diagnosis was businessman and philanthropist E. Bronson Ingram, namesake of the Vanderbilt-Ingram Cancer Center, who died of CUP in 1995.

The underlying mystery and the paucity of effective treatment options make it a diagnosis all the more frightening and maddening for patients and families.

“When I went to the library for information about breast cancer, there were shelves and shelves of it,” Ardythe says. “When I went to the library to learn about cancer of unknown primary, I found mention of it in the index of a few medical books, and that led to only a few paragraphs.”

Ardythe and Frank weren’t ready to accept the grim prognosis. They went to a well-known cancer center for a consultation. There, doctors recommended a particular treatment and used a tumor in Frank’s jaw as a “marker” for whether it was effective. After three sessions, the tumor had grown. It wasn’t working. Nearly three dozen radiation treatments to the jaw followed. The side effects from the radiation were the worst of all, Ardythe says.

“Next, they did a complete bone scan,” she recalls. “There were tumors everywhere. Now there really was no hope. One night, the bone in his arm cracked as he lay down in bed. Any other bone could break at any time. We were terrified.”

The family called hospice. “With the wonderful help of our children, Cheryl and Tim, we were able to keep Frank at home,” Ardythe says.

Shortly after the seriousness of Frank’s illness became known, a group of scientists and friends began planning an honorary seminar and early 75th birthday party. The invitees were from all over the country and some from abroad.

“Hearing about the plans gave Frank such a lift,” Ardythe recalls. “He felt very loved and admired, which he was.”

Frank died two weeks before the event. The seminar was held and the birthday celebration became a memorial service, with more than 100 guests.

“One of the letters written to me after Frank’s death came from a man whose father had died of the same diagnosis and lack of treatment 23 years ago,” Ardythe says. “It made me both sad and angry. Nothing had changed in 23 years!”

During this time, Ardythe called Vanderbilt-Ingram in her search for information. She was connected with Jennifer Pietenpol, Ph.D., who had just become interim cancer center director at the time. “She helped me understand the whole process and was so personally involved with her sympathy and understanding,” Ardythe recalls. “That’s when we heard about Vanderbilt’s Discovery Grant Program,



and it seemed a perfect way to have something positive come out of our experiences.”

The Discovery Grant in Research for Cancer of Unknown Primary in Loving Memory of Frank Jones, Ph.D., was established by Kenneth and Ann Jones, Frank’s brother and sister-in-law. So far, 60 people have contributed to this grant, which is designed to generate high-risk discoveries that can be then used to leverage greater support from federal grants.

This grant will fund research at Vanderbilt-Ingram into how cancer spreads to and destroys bone, a significant consequence of CUP. In fact, in many patients with CUP, the majority of “tumor burden” – the total amount of cancer in the body – is in the bones.

Gregory Mundy, M.D., John A. Oates Chair in Translational Medicine and director of the Vanderbilt Center in Bone Biology, and his colleagues are working to understand the specific biologic mechanisms responsible for bone metastasis. The ultimate goal is to develop new approaches to prevent bone destruction, fractures, pain, and tumor spread and growth.

Specific projects include:

- Research in animal models of human cancer to understand exactly how – at the molecular level – cancers destroy bone.
- Collaborations with scientists in the Vanderbilt School of Engineering and at Oak Ridge National Laboratory to study effects of cancer on bone quality and fragility.
- Studies to determine how bone cell activity can affect cancer cell growth. The team has found that drugs that alter bone cell activity also make cancers grow less well in bone.

“Ultimately, the objective is to develop effective approaches to improve both survival and quality of life for patients with cancer metastases in the bone, and potentially to develop ways to prevent this devastating spread of cancer,” Mundy said. “While this knowledge will benefit patients with other types of cancer that spread to the bone, the group that may benefit the most will be those who face cancer of unknown primary. This approach has been shown over the past decade to improve the quality of life with other cancers that frequently involve bone, such as breast cancer and myeloma.”

Ardythe remains hopeful that the work will yield answers and treatments to help families in similar situations. And she hopes for more information and resources, including a comprehensive Web site, for families facing this complex and devastating diagnosis.

“Cancer care should be a group effort, including all relevant medical professionals and patients and families,” she says. “I hope someday that everything learned can help others face this horrible disease with more understanding.”



For more information about cancer of unknown primary and doctors at Vanderbilt-Ingram Cancer Center who treat CUP, log on to www.vicc.org, click on cancer types and go to carcinoma of unknown primary. Or call our Cancer Information Program at (800) 811-8480.

PHOTO BY DAVID HILLS



At the Jones’ home in Silver Spring, Md., Ardythe Jones and the couple’s children and grandchildren share memories of a husband, father and grandfather who “loved to analyze and explore ideas, talk and tell jokes, and read.”

CANCER OF UNKNOWN PRIMARY (CUP)

This diagnosis is made when a tumor is found and its location and appearance suggest that it started somewhere else in the body, but the original location is never found.

The National Cancer Institute estimates that 2 percent to 4 percent have CUP – as many as 56,000 Americans this year will be diagnosed with CUP.

CUP is slightly more common among men than women, and the average age of patients is about 60.

Overall, this is a very dangerous cancer. Only about half of patients will live 9-12 months after diagnosis.

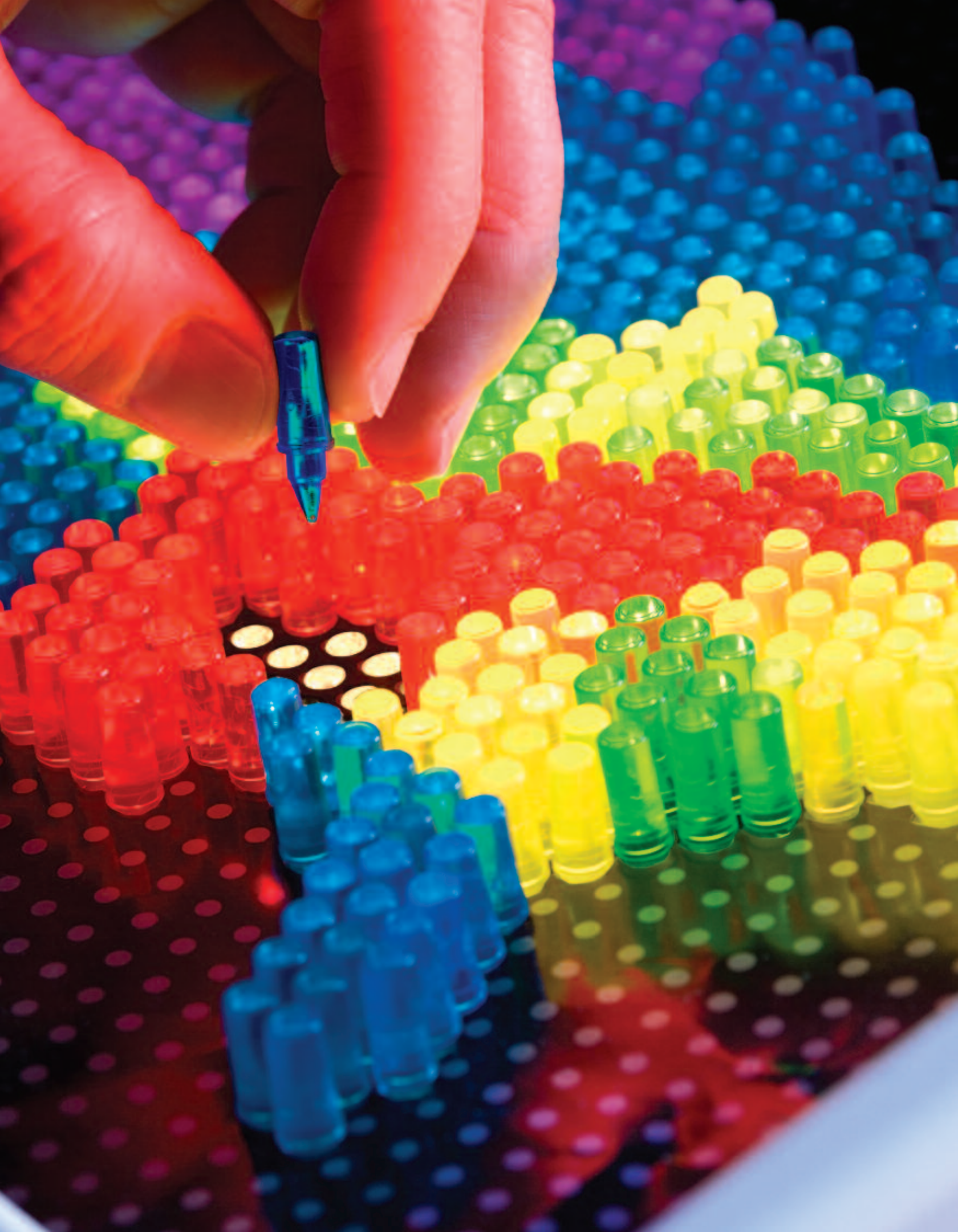
There are several reasons why CUP is so serious:

- * Most are fast spreading.
- * Because the exact type of cancer is not known, it more difficult for doctors to know what treatment is likely to help.
- * Because the cancer is usually widespread, it is rarely curable.

What does the future hold for CUP?

Because CUP is not one specific type of cancer but rather a diverse group of many types of cancers, the greatest progress against CUP is likely to depend on continued advances in the understanding of the molecular basis of all cancers. Scientists at Vanderbilt-Ingram and other leading cancer centers are learning more every day about how changes in a person’s DNA can cause normal cells to develop into cancer. A greater understanding of the genes (regions of a person’s DNA) involved in these abnormalities is shedding into how and why this transformation occurs.

Someday, doctors may be able to take a sample of CUP, analyze its patterns of genetic expression and compare those patterns against the patterns of known cancers to help determine its origin.



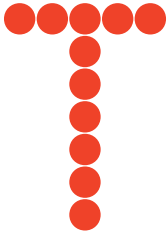


the cancer belt

WHERE YOU LIVE CAN IMPACT YOUR RISK

The South is known for many things – hot, steamy summers, iced tea laced with sugar and friendly people with a tendency to welcome strangers. ● But beneath the veneer of Southern hospitality and gracious living lurks a silent killer. Cancer is more prevalent in the South, and death rates, especially among African-Americans, are alarmingly high. Cancer researchers have their own name for the Southern region of the United States – The Cancer Belt. ● Brain cancer is just one of the malignancies disproportionately affecting people who live in Southern states. Glioma, also known as glioblastoma, may be rare but it is lethal. Ninety-five percent of patients die within two years of diagnosis. ● “When you look at a map of brain cancer incidence in the United States, the Southeast just lights up in red,” said Reid Thompson, M.D., associate professor and vice-chair of the Department of Neurological Surgery. “When we found this hot-spot on the National Cancer Institute’s mortality maps, we realized something unusual is going on in this region.”

By Dagny Stuart | Photograph by Dean Dixon



hompson and co-investigator Kathleen Egan, M.P.H., Sc.D., have launched a study to find clues that may explain this brain cancer cluster. (Egan, formerly of Vanderbilt-Ingram Cancer Center, is now on faculty at the H. Lee Moffitt Cancer Center and Research Institute in Tampa, Fla.) Vanderbilt-Ingram, along with four other cancer centers in the region, will enroll as many as 1,000 patients in the federally funded initiative.

“We’re asking patients about their diets, possible job-related exposure to cancer-causing chemicals and we’re collecting DNA samples,” explained Thompson, who also serves as director of Vanderbilt’s Brain Tumor Center. “We know there are some genetic markers that are linked to other forms of cancer and they may play a role in brain cancer, as well.”

Brain cancer isn't the only cancer taking an unusual toll on Southern populations. Several forms of cancer strike Southerners more often than people who live in other sections of the country. Topping the list is lung cancer. Despite decades of warnings about the dangers of cigarette smoking, Southerners continue to smoke more than those in other regions of the country and, as a result, they are far more likely to be diagnosed with lung cancer.

Cancers of the mouth and throat also are linked to tobacco use, and once again those cancers are more prevalent in Southern states.

“Instead of cigarettes, it is the use of snuff and chewing tobacco – among women as well as men – that causes this spike in oral cancers,” according to William Blot, Ph.D., professor of Medicine. “There are still parts of the South, especially rural areas, where snuff use is fairly common among women.”

Behavior like tobacco use is clearly linked to the development of some forms of cancer. But it is less easy to explain why people living in the South are developing many types of cancer at higher rates than folks who live in other regions of the country. And it doesn't explain why African-Americans are more likely to develop some forms of cancer and are more likely to die from the disease.

So Blot is leading the Southern Community Cohort Study (SCCS), the largest epidemiologic study in history to explore why the South has become the Cancer Belt and why African-Americans

INCIDENCE OF LUNG CANCER

cases per 100,000 people

Kentucky 99.5

Tennessee 82.2

New Jersey 62.1

New York 63.5

Source: Centers for Disease Control and Prevention, 2004

experience higher rates of many types of cancer. Starting with a \$28 million grant from the National Cancer Institute, the SCCS hopes to recruit 90,000 people in 12 Southern states to learn about their lifestyles, their medical histories and their risk factors for cancer and other serious diseases. Two-thirds of the participants will be African-American and many will be from rural areas.

The SCCS is a collaborative project among Vanderbilt-Ingram, Meharry Medical College and the International Epidemiology Institute, as well as participating community health centers across the South.

“The study participants form one of the groups at highest risk for cancer that has ever been studied,” explained Blot. “Most other investigations have not included large numbers of African-Americans and few have included low-income individuals and people from rural parts of the country. This is the first large-scale study and the first in the South to include large numbers of all of those groups.”

■ ■ ■ All in the Family ■ ■ ■

The SCCS is designed to be a longitudinal study of this Southern population cohort. Each participant is interviewed and asked about their family background, medical history, diet, smoking habits and work environment. Every four years, researchers will do follow-up interviews, looking for new cancer cases or other diseases and trying to find the patterns of behavior, exposure to carcinogens or other clues that could explain why cancer is so prevalent in the region.

Alice Smith of Antioch, Tenn., was determined to sign up for the study when she visited the Matthew Walker Comprehensive Health Center in Nashville because cancer has forged a deadly legacy in her African-American family.

“Cancer took out the majority of the women on my mother’s side of the family, so whenever there is anything to do with cancer I always get involved,” she explained. Smith, 54, says her mother, grandmother, sister and several aunts were diagnosed with various types of cancer including breast, throat and pancreatic cancer.

“The doctors keep saying it’s hereditary, so I try to eat healthy and take care of myself,” said Smith. She also sees her doctor often, especially after she was diagnosed with multiple sclerosis. She hopes that her participation in the SCCS will help scientists determine the factors that contribute to so many serious illnesses in her own family and other families across the South.

“If they can figure out what’s causing it, they might be able to find some things you can do to prevent it,” Smith said with hope in her voice. “I’m very concerned about my health because I want to be here for a long, long time.”

■ ■ ■ Cancer in the Neighborhood ■ ■ ■

The focus on African-Americans is long-overdue, especially since this group has much higher mortality rates for many forms of cancer. Even when the incidence of a certain form of cancer is higher



PHOTO BY TAMARA REYNOLDS

TENN. PROSTATE CANCER INCIDENCE

cases per 100,000 people

Black men 178.9

White men 108.9

TENN. PROSTATE CANCER DEATH RATE

cases per 100,000 people

Black men 71.2

White men 28.9

Source: Tenn. Department of Health, 1997-2003

Beech points to a 2002 study on unequal treatment by the Institute of Medicine which found clear-cut evidence that longstanding racial attitudes affect patient treatment.

“The literature has consistently shown this disparity in treatment and access,” Beech said. “The IOM report demonstrated that even when providers are presented with fictitious patients with the same patient profile, with race as the only difference, physicians often provided a different diagnosis, different prognosis and different course of treatment for the patients.”

■ ■ ■ Genes Play a Role ■ ■ ■

While lifestyle factors and access to preventive surveillance and treatment play a role in cancer, scientists increasingly are finding genetic differences that may explain some of the disparities.

Consider the surging number of prostate cancer cases among African-American men compared with white men.

African-American men are far more likely to be diagnosed with prostate cancer than white men, and the death toll is even more alarming, with African-Americans more than twice as likely to die from the disease. Researchers discovered a combination of genes that appear to play a role in the aggressive forms of the disease often found among black men.

The skin pigmentation differences associated with race may play more than a cosmetic role in some forms of cancer. Dark pigmentation may hinder and light skin may help the body's ability to produce vitamin D.

“It’s been speculated for a number of years that vitamin D may play a protective role in cancer,” Blot explained. “Researchers have found lower blood levels of vitamin D among people living at northern latitudes, and those populations are more likely to develop certain forms of cancer. Since we know that exposure to sunlight helps the body produce vitamin D, it stands to reason that someone with dark skin may not be getting enough of the vitamin. Our study in the South found roughly half of the African-American population had insufficient levels of vitamin D versus only 10 to 15 percent of the white population.”

Healthy lifestyle habits – eating more fruits and vegetables, eating less fat and being more physically active – can reduce risk of cancers. But these habits may be more challenging for folks in low-income areas, and this may contribute to cancer disparities, says Bettina Beech, Dr.P.H. (above).



If researchers can determine exactly how vitamin D influences cancer risk, they may be able to supplement the diets of those who have insufficient levels of the vitamin.

This search for genetic variables is just one of the reasons the Southern Community Cohort Study includes DNA samples. Each participant is asked for a blood and urine sample. Those who prefer not to give blood are asked to use a mouth rinse, from which researchers can extract DNA. The samples collected in all 12 states are shipped to Vanderbilt for long-term secure storage.

This database of biologic specimens serves as a treasure trove for scientific investigators. With each new discovery, researchers can study the intricacies of those DNA samples, looking for the patterns that confirm or refute the new findings.

"Collecting those specimens is absolutely critical to the success of this project," Blot enthused. "The way biology and medicine are moving, eventually we're going to be in a world of individualized

medicine, individualized treatment and individualized prevention. To do that you really must have biologic information on patients."

The discoveries unearthed by this and other studies of human biology should play a role in enhancing cancer care, especially for people living in the South. But that same information must be used to draw a new roadmap for delivery of high-quality care to every demographic group.

"It is essential that everyone benefit from this kind of high-impact scientific research," said Jennifer Pietenpol, Ph.D., professor of Biochemistry and director of Vanderbilt-Ingram. "We owe it to our patients and to future generations to ensure that the lessons we learn as scientists are shared with everyone who walks through our doors." •



Learn more about the Southern Community Cohort Study at www.southerncommunitystudy.org.

■ ■ ■ CLERGY, CENTER JOIN TO 'KICK BUTTS' ■ ■ ■

Nashville, Tenn., sits snugly in the center of the Bible Belt, that swathe of Southern states where religion is intricately woven through the fabric of daily life. So when Vanderbilt-Ingram Cancer Center researchers and local African-American civic leaders started talking about health problems linked to tobacco, they naturally turned to a local pastor for guidance.

The Rev. Raymond Bowman, pastor of Spruce Street Missionary Baptist Church, had his own reason for agreeing to lead an anti-tobacco education campaign. His own father was diagnosed with cancer nearly 30 years ago.

"We believe it is because he started smoking when he was 7 or 8 years old, down in Mississippi," Bowman explained. "The cancer keeps on recurring and it has caused him so much pain over the years. My goal in working with Vanderbilt-Ingram and the National Association for the Advancement of Colored People (NAACP) is to prevent other people from having to live through the horror of watching a loved one suffer because they made some bad choices early in life."

As part of the NAACP Tobacco Prevention Initiative, Bowman called on other pastors in the African-American community to take concrete action against tobacco use among members of their congregations. They called their project the Kick Butts program.

In November 2006, in conjunction with the American Cancer Society's Great American

Smokeout, 15 pastors in the Kick Butts program gathered to sign a proclamation designating their churches as smoke-free facilities. Nashville's Metro Public Health Department agreed to provide anti-smoking signs for every church that participated.

Elizabeth A. Williams, Ph.D., associate director of Minority Affairs for Vanderbilt-Ingram, was one of the researchers who helped formulate the strategy for the community campaign.

"We were able to bring scientific knowledge to bear on the discussion about tobacco use," said Williams. "In addition to the smoking proclamation that first year, there also was an anti-tobacco sermonette offered by one of our clergy partners about the impact of tobacco on communities of color. We developed this educational program to coincide with an existing training congress made up of nearly 40 Baptist congregations in the Nashville area. So we took an existing event and infused it with an anti-tobacco message."

The clergy leaders decided they wanted to do far more than make a statement with just one event. They wanted to create beneficial and long-lasting changes in their community.

"It felt like we asked for tap water and they gave us Perrier instead," said Tonya Micah, manager of the Office of Minority Affairs at Vanderbilt-Ingram.

As a result of the partnership among the NAACP, Vanderbilt-Ingram, Meharry Medical

College, Metro Government and Tennessee State University, the Kick Butts program has expanded to include educational workshops for adults and children. The organization's leaders also are studying advertising patterns in their neighborhoods and are planning to communicate with tobacco companies and advertising agencies about the seemingly high rate of tobacco advertising in the area.

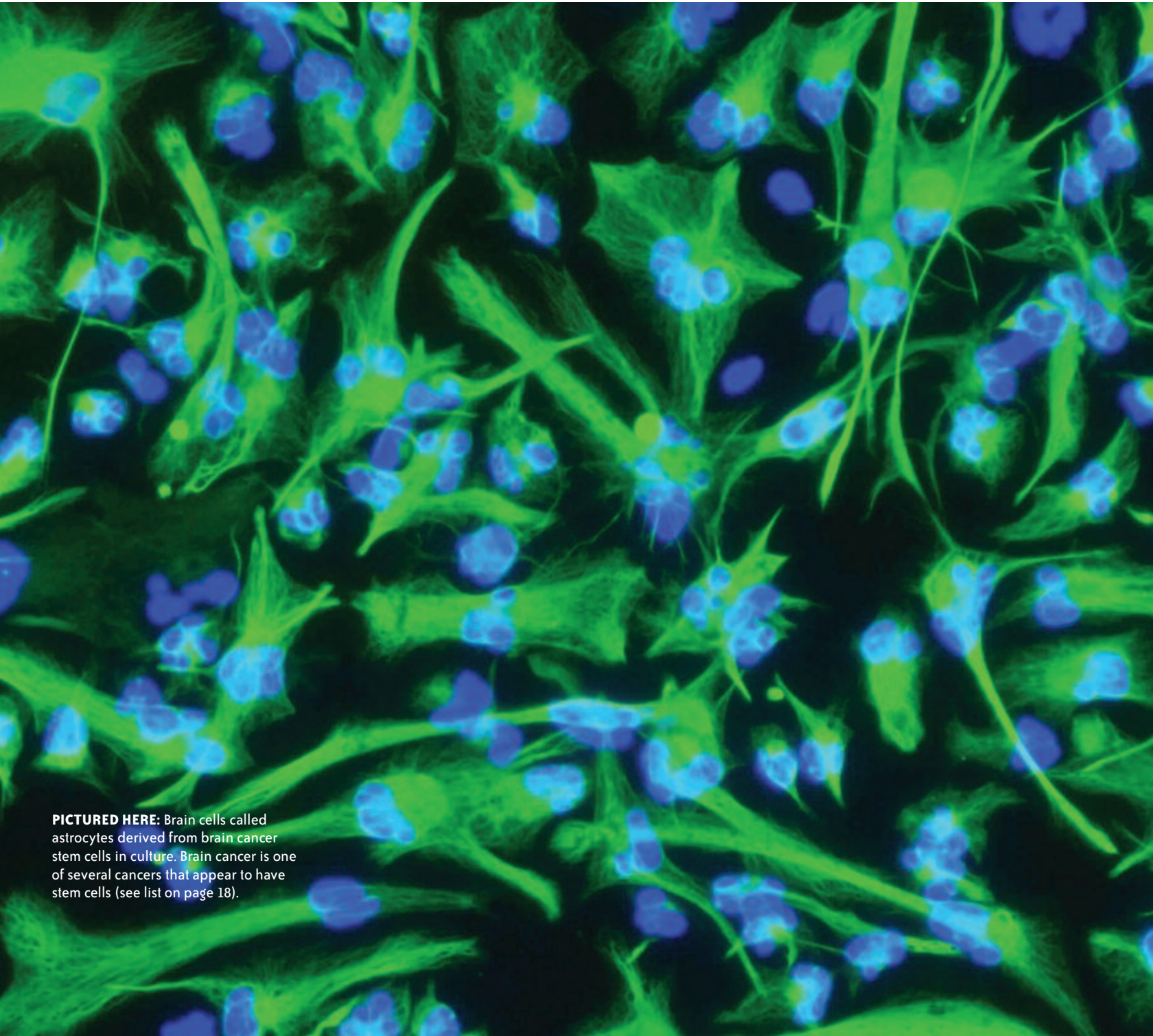
As part of her academic research, Williams will be measuring the impact of this unique community-driven education program.

"As a group, we developed needs assessment surveys for adults and youth to get prevalence data about their tobacco use as well as their exposure to tobacco advertising," Williams explained. "We plan to implement a pilot project in many of our churches that includes a tobacco prevention program for youth. All of these prevention models will be evidence-based so they will include pre- and post-test instruments to determine the level and extent of behavioral change."

Bowman is determined to spread the word about the health threat from tobacco and to spare others the pain his family has endured.

"If you want people to be healthy and strong then you have to be advocates to make sure they live productive lives," he said.

— by Dagny Stuart



PICTURED HERE: Brain cells called astrocytes derived from brain cancer stem cells in culture. Brain cancer is one of several cancers that appear to have stem cells (see list on page 18).

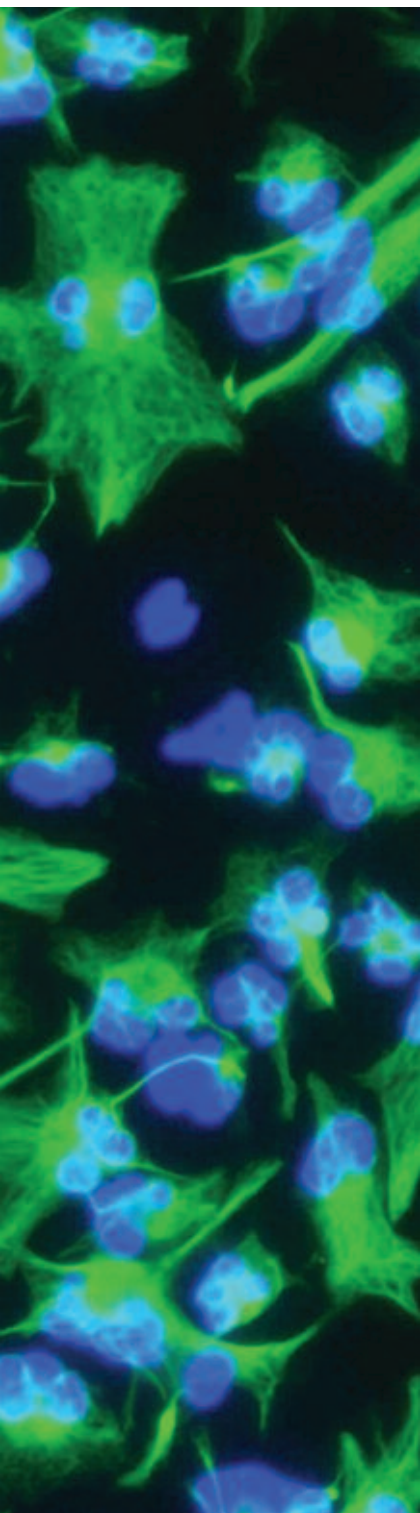


Pulling
Cancer's

ROOTS



IF A GROWING NUMBER OF
PHYSICIANS AND SCIENTISTS
ARE RIGHT, CANCER STEM
CELLS MAY BE THE BEST
TARGET YET FOR
ELIMINATING TUMORS



*By Leigh MacMillan
Image by Steven Pollard/Wellcome Images*



Every gardener knows that to truly eliminate a weed, you have to pull out the root.

Nip the weed off at the surface only, and in time it will grow back. Such might also be the case with cancer – treatments aimed at shrinking tumors may be leaving behind the “roots,” a core of cells with the unique capacity to regenerate the tumor. Proponents of the idea call it “the dandelion phenomenon,” and they argue that new treatments need to target these “cancer stem cells,” which appear to be present in a wide variety of tumor types. Clinical trials that aim to extend patient survival by killing these cells are under way.

“Within two to three years, we’re going to have clinical trials to treat almost every kind of common cancer with an agent that we think targets cancer stem cells,” predicts Max Wicha, M.D., director of the University of Michigan Comprehensive Cancer Center and a leading expert on cancer stem cells. “The real proof that cancer stem cells are clinically important will be in the results: do the patients do better than with our current therapies?”

The cancer cell, stem cell connection

In 1875, the pathologist Julius Cohnheim suggested that stem cells misplaced during embryonic development give rise to tumors in adult life. Over the course of the next century, scientists increasingly recognized that cancer cells and normal stem cells share certain properties, chief among these their seeming immortality.

Normal stem cells populate the tissues of the developing organism and maintain and regenerate tissues throughout life. They have two defining characteristics: they can divide nearly indefinitely to produce more copies of themselves – the immortality that scientists call self-renewal – and they can produce daughter cells that mature into various cell types.

Embryonic stem cells, which are perhaps the most versatile of stem cells, have made news headlines and sparked political controversy since

they were first isolated from human embryos a decade ago. Because embryonic stem cells normally generate all of the diverse cell types in the organism, they are a tantalizing source of healthy cells for repairing diseased tissues. And while it might be possible in the future to direct their maturation for cell-based therapies, clinical “stem cell” applications may come first from killing their dark twins – the cancer stem cells that replenish and renew tumors.

“I believe there will be benefits on both sides, but I think we’ll know sooner if targeting cancer stem cells has a clinical impact than we’ll know how to direct stem cells to replace damaged tissues,” Wicha says.

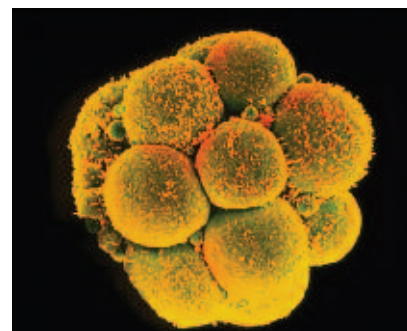
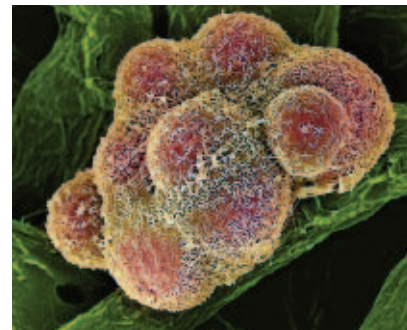
Mark Magnuson, M.D., director of Vanderbilt’s Center for Stem Cell Biology, says that the two areas of stem cell research are cross-fertilizing and informing each other.

“Everything we’re learning about normal stem cells – what they are, how they grow, what genes confer ‘stemness’ – these are all interesting findings that are transforming our understanding of stem cells in general and that have relevance to both normal and cancer stem cells,” he says.

All cancer cells are not created equal

Although the idea that a small population of cancer cells has stem cell-like properties is more than a century old, the technologies for identifying these rare cells were only recently developed.

Using flow cytometry – a method for sorting living cell populations based on cell surface proteins – and a mouse model for growing



Cancer stem cells, bottom, may be thought of as the “evil twin” to embryonic stem cells, top. They share some similar traits, including immortality, and knowledge of one can help inform knowledge of the other, experts say.

PHOTO RESEARCHERS, INC.

Mark Magnuson, M.D., director of Vanderbilt's Center for Stem Cell Biology, says the cancer stem cell is not yet clearly defined. Do they come from normal stem cells? Or do they develop from other cells that have regained their power of self-renewal?

human blood stem cells in mice, John Dick, Ph.D., and colleagues at the University of Toronto began to identify cancer stem cells in leukemia in the 1990s.

The investigators reported in a widely cited 1997 *Nature Medicine* paper that only a fraction of human leukemia cells could reproduce leukemia in a mouse. These cancer stem cells were selected based on certain cell surface proteins, and they represented less than one in 10,000 of the human leukemia cells. The leukemia that was produced in the mice shared the diversity of cells present in the original leukemia, supporting the idea that the cancer stem cells could both reproduce themselves and give rise to various mature cell types.

Evidence that solid tumors also contain cancer stem cells was first reported in 2003. Michael Clarke, M.D., Wicha, and colleagues at the University of Michigan used surface proteins to sort cells from human breast tumors. They showed that only one sub-population of cells was able to re-create the original tumor in mice. As few as 200 of these breast cancer stem cells, which represented between 1 percent and 10 percent of the original tumor, could form tumors, whereas 20,000 cells isolated from the same tumor but without the same cell surface characteristics did not form tumors.

Since then, cancer stem cells have been identified in a range of tumors including brain, colon, head and neck, prostate and pancreas.

"It appears that virtually all cancers have only a small component of cells that is capable of transferring the cancer in a mouse model;



PHOTO BY DEAN DIXON

they're likely the only cells that are really tumorigenic, that are driving the cancers," Wicha says.

Cancer-in-waiting

Even though many types of tumors appear to have sub-populations of cells that can regenerate the tumor with all of its diverse cell types, the cancer stem cell hypothesis is still debatable.

"Currently, there's no clear definition of what a cancer stem cell is," says Susan Kasper, Ph.D., assistant professor of Urologic Surgery and Cancer Biology at Vanderbilt. "Cells identified as cancer stem cells appear to have a few cell surface markers in common, but one of the key challenges in the field is to define the characteristics of the cancer stem cell."

Magnuson agrees. "The research related to cancer stem cells is all tumor-based. And the problem is you really don't know what the stem cell in the tumor is," he says.

Cancer stem cells might come from normal stem cells, when mutations dismantle the normally tight controls on their self-renewal



Cancers that appear to have stem cells:

BRAIN
PROSTATE
BREAST
PANCREAS
COLON
LEUKEMIAS
HEAD AND NECK
MYELOMA
OVARY
MELANOMA
LIVER
SARCOMAS

Susan Kasper, Ph.D., and colleagues have developed human prostate cancer stem cell lines to answer many questions: How do they arise? How do they survive and multiply? Are they really at the core of a tumor?



PHOTO BY ANNE RAYNER

properties. They might also come from mutations that restore the power of self-renewal to so-called progenitor cells, the offspring of stem cells that mature into certain cell types.

Both normal stem cells and progenitor cells, because of their long-lived natures – stem cells could be around for an entire lifetime – have the potential to accumulate the multiple mutations required for carcinogenesis. The hypothesis is appealing as an explanation for how tissues with very short-lived mature cells, like the blood, skin, and lining of the gut, can accumulate enough mutations to give rise to a tumor: the mutations happen in the long-lived stem/progenitor cell population.

A cancer stem cell can be thought of as lurking in the general stem cell population, Kasper explains. Once it has accumulated a number of mutations, it's there "waiting for the right stimulus to activate it so that it begins proliferating."

"No one knows what those signals are – we talk about cancer stem cells and how they might work, but very little is known about the biology of cancer stem cells," she says. "For example, how do these cells arise? How do they survive and proliferate? Is the core of a metastatic lesion a cancer stem cell?"

Kasper and colleagues have developed human prostate cancer stem cell lines (cells that can be grown in the laboratory indefinitely) that they will use to address these kinds of questions.

Are cancer treatments off target?

The cancer stem cell hypothesis, if correct, could explain why many cancer treatments don't improve long-term patient survival. Treatments are selected for their ability to cause tumor shrinkage, which doesn't necessarily predict improved survival.

"We've basically designed a lot of treatments that kill the wrong cells in the tumor," Wicha says. "The treatments leave the cancer stem cells behind, and those cause recurrence."

Wicha cites evidence from animal models and from ongoing studies in patients with breast and pancreatic cancer. He and colleagues have examined the cells that remain after chemotherapy and radiation therapy shrink the tumors.

"If you transfer those cells that are left to a mouse, they grow like crazy," he says.

Cancer stem cells may be more resistant to cancer treatments because of the properties they share with normal stem cells: slow cell division cycles (cancer therapies often target rapidly dividing cells) and high levels of proteins that protect against DNA damage and cell death.

These shared properties may also lead to the development of novel therapies that act across many different tumor types. Signaling pathways that are important for normal stem cells during development, such as the Wnt, Hedgehog and Notch pathways, also appear to be important regulators of cancer cell growth.

"What we learn about one cancer stem cell in one kind of tumor is informing us about what's going on in another kind of cancer stem

"If we develop an effective therapy for one kind of cancer – and that's a big if – it might be effective in killing stem cells in another cancer too."

Max Wicha, M.D., director of the University of Michigan Comprehensive Cancer Center

cell," Wicha says. "If we develop an effective therapy for one kind of cancer – and that's a big if – it might be effective in killing stem cells in another cancer too."

Clinical trials of existing drugs or unique combinations of drugs that target surface proteins on cancer stem cells are already ongoing for multiple myeloma and leukemias.

And Wicha and colleagues at the University of Michigan, along with investigators at the Dana-Farber Cancer Center and Baylor College of Medicine, are gearing up for the first clinical trial targeting cancer stem cells in a solid cancer. The trial will test an inhibitor of the Notch signaling pathway in breast cancer. The drug, developed by Merck, kills breast cancer stem cells in laboratory studies.

The ultimate test: survival

Clinical trials of cancer stem cell-directed therapies face challenges. Will the treatments kill normal stem cells that are important for tissue maintenance and regeneration? What are the measures of success for a treatment that's directed against a tumor's slow-growing "roots" rather than its visible "weed?"

The potential for killing normal stem cells is perhaps the biggest challenge to the field, Wicha says. There are data now being published that support the notion that cancer stem cells may have different sensitivities to certain drugs, even though the drugs target pathways that are also active in normal stem cells.

"The extra mutations in the cancer stem cell may make it particularly vulnerable to certain kinds of treatment that don't affect a normal stem cell," Wicha says. "That remains to be proven. The real test will be in giving these agents to patients; we'll be watching very carefully for side effects."

Tumor shrinkage is a traditional measure of success for cancer therapies. But cancer stem cell-targeted treatments may not have any



PHOTO BY LIN JONES, UNIVERSITY OF MICHIGAN

If the cancer stem cell hypothesis proves correct, it could explain why many treatments don't improve long-term survival. "We've basically designed a lot of treatments that kill the wrong cells in the tumor," suggests Max Wicha, M.D., (above). "The treatments leave the cancer stem cells behind, and those cause recurrence."

visible effects on the bulk of a tumor. One notion is to first use another agent to "de-bulk" the tumor and induce remission, and then follow with a cancer stem cell-targeted agent, using duration of remission as a measure of success. Investigators are also exploring alternate laboratory-based tests.

Ultimately, the question is – are cancer stem cells truly the cells that regenerate the tumor, and if they are killed, does that eliminate the cancer and improve survival?

Measuring survival takes a long time, which is why investigators are designing alternate tests. They will eventually have to prove that these quicker measures "correlate with patients living longer – that's the ultimate test for any therapy," Wicha says.

"I hope that people won't get discouraged if the first trials don't work," he adds. "We're really just at the beginning of this, and I think the idea is right."

Roundup, anyone? 🍷



web link

Learn more about Vanderbilt's Center for Stem Cell Biology at www.vcsb.org.





Found in Translation



DELIBERATE APPROACH TRANSFORMS DISCOVERY
INTO TREATMENT ADVANCES

By Dagny Stuart
Photography by Tamara Reynolds

Sometimes an accident can be a good thing. Sometimes an accident saves lives.

Just ask Teresa Lundberg, a Mt. Juliet, Tenn., cancer survivor who believes her life was saved because her breast cancer was treated with a drug called Herceptin.

“My mom dying of lung cancer was my last experience with cancer,” explained Lundberg. “Through the grace of God I was urged to get a second opinion. Dr. Mark Kelley and Vanderbilt-Ingram Cancer Center were highly recommended through various sources. Then I was blessed to be assigned to Dr. David Johnson and Dr. Julie Means, my oncologists. They said my tumor was HER2 positive, which meant there was something that was telling it to grow at a faster rate. I wanted to do whatever I could to stop it, and they gave me hope that that could be accomplished.”



topping the tumor's growth was possible because of a series of happy accidents in the laboratory years earlier that revealed why tumors grow, and led to the development of drugs to halt that growth. Nobel Laureate Stanley Cohen, Ph.D., Vanderbilt distinguished professor of Biochemistry Emeritus, started the chain of discovery – and translation of that discovery – that led to the development of Herceptin.

Cohen, along with Viktor Hamburger, Ph.D., of Washington University, and Italian scientist Rita Levi-Montalcini, Ph.D., was investigating nerve growth in chick embryos in the early 1960s. They injected the embryos with an extract from snake venom, thinking that it would stop nerve growth. Instead they were amazed to see an array of new nerve fibers. Eventually, Cohen tried injecting related extracts into baby mice. Not only did the nerves grow, Cohen noticed something equally remarkable. The baby mice opened their eyes several days earlier than normal. The extract was making skin cells grow faster, allowing the eyes to open early. The same thing happened with human skin cells.

Cohen realized immediately that he had stumbled on something revolutionary. “There are very few ways you can improve on nature and make it go faster,” he explained. Eventually Cohen isolated a protein that made the baby mice open their eyes early. It was named epidermal growth factor or EGF because it makes the epidermis or top layer of skin grow.

What started as an interesting theoretical exercise resulted in Cohen’s “aha” moment, and it launched decades of research by cancer scientists who realized that EGF plays a role in cell growth, including cancer cells. Since cancer is the result of uncontrolled cell growth, finding a way to block that growth is key to treating the disease.

By the 1980s other scientists investigating brain tumors in rats found that a nearly identical cancer-causing gene (oncogene) existed in humans and was present in excessive amounts in about 20 percent of breast cancers. The product of that gene was a receptor that was firing signals for cancer cell growth. Once found, investigators finally had a target for breast cancer – the HER2 receptor. They immediately focused on developing a drug that could block the HER2 receptor. Herceptin is that drug and it is saving the lives of some women whose breast cancer is positive for the HER2 receptor.

Teresa Lundberg was one of the patients enrolled in one of the clinical trials that proved Herceptin could make a difference. “I felt it was another avenue out there to help my chances,” she said. “I didn’t

want to sit back and feel that I had not done everything I could to go after this cancer.”

Halfway through that trial, researchers determined Herceptin was showing such strong results it became part of the standard treatment regimen for every woman in the trial. Today, oncologists routinely test breast cancer patients to find out if their tumor is positive for the HER2 receptor. The test not only identifies women who should benefit from the drug, it prevents women who are negative for the HER2 receptor from being exposed to a therapy that is unlikely to work.

“We wouldn’t have these treatments if somebody hadn’t been working in the lab,” said Lynn Matrisian, Ph.D., professor and chair of the Department of Cancer Biology. “I don’t know if people understand how much time, thought and effort, and trial and error, go into figuring out which discoveries are going to be translated.”



‘We are less in the dark this way’

While serendipity will always play a role in biomedical discovery, translational research is a deliberate approach to transform scientific discoveries from the laboratory into clinical applications for patients –

PATIENTS AS PARTNERS



While scientists may drive cancer research efforts, at Vanderbilt-Ingram cancer survivors are invited to help steer the research vehicles. The Research Advocacy program is designed to close the translational research circle by bringing the patient perspective into research discussions.

“Around the time we received our first Lung Cancer SPORE grant one of my patients and the wife of a patient became very interested in the research here,” recalled David Carbone, M.D., Ph.D., professor of Medicine and Cancer Biology. “Back in 2001 the concept of patient advocates was not well-formulated, but I started inviting them to our research meetings. This is a life-and-death struggle for these patients and their families and they need to be empowered, they need to be informed, and the best way to accomplish that is to ask questions and go to the meetings and inspect the research process.”

Today, there are 12 research advocates who work directly with Vanderbilt-Ingram’s three SPOREs – Specialized Programs of Research Excellence – in gastrointestinal (GI), lung and breast cancers.

Nancy Roach became an advocate for GI cancer research after her mother-in-law was diagnosed with rectal cancer. “I saw the groundswell of support for breast cancer funding and the research breakthroughs and I got frustrated that the same kind of focus wasn’t there for colon and rectal cancer,” explained Roach.

When she was diagnosed with cervical cancer a few years later, the



and to take information from the clinic or patient bedside back to the laboratory for exploration.

“Translational research is mechanism-based research that is applicable to patient care,” explained Carlos L. Arteaga, M.D., professor of Medicine and Cancer Biology, and director of Vanderbilt-Ingram’s Breast Cancer Specialized Programs of Research Excellence (SPORE) grant funded by the National Cancer Institute. “We now have biomarkers or targets that we are identifying in tumors, and we have developed drugs to hit those targets. Since we know what the drug hits and we know how it works, we are in a position to understand why it doesn’t work in some cases. We are less in the dark when we do things that way and can provide more information so patients and their doctors can make a more informed decision.”

This search for biomarkers identified in the laboratory produced another new drug, Gleevec, which is showing significant results in many patients with chronic myeloid leukemia. This blood disease occurs when pieces of two chromosomes break off and swap places on the opposite chromosome. This chromosome mix-up causes a blood cell protein to be turned on all of the time, telling the bone marrow to make too many abnormal white blood cells. Gleevec blocks that signal.

“Gleevec is a beautiful example of a targeted therapy and it got everyone in the cancer field excited,” according to Matrisian. “It is a



PHOTO BY TAMARA REYNOLDS

Lynn Matrisian, Ph.D., is now spending half her time at the National Cancer Institute spearheading the effort to streamline oversight and funding of research designed to translate exciting discoveries for the benefit of patients.

fight became even more personal. “I thought I knew what it was like to hear the words ‘you have cancer’ and grapple with my own mortality, but I didn’t until I went through it.”

Today, Roach is one of many patient advocates who sits in on numerous research meetings at Vanderbilt-Ingram and asks questions on behalf of patients. She has formed her own national advocacy group – C3: Colorectal Cancer Coalition – and she continues to highlight Vanderbilt-Ingram as a leader in the patient advocacy movement.

“One of the things I really like about the Vanderbilt researchers is that when I ask why they’re doing a certain type of clinical trial, they always have very clear answers and it’s always something that makes a difference for patients.”

Advocates at Vanderbilt-Ingram have contributed in a variety of ways including reviewing and providing input on research development and design, clinical trials, informed consents and tissue collection, providing a strong voice for the priorities and needs of patients.

Lynne Cargen is an 11-year cancer survivor who serves as a research advocate for the Breast Cancer SPORE program. She was just 39 when she was diagnosed with invasive breast cancer.

“We are there to put a face on the disease and to show the reality to the researchers,” Cargen explained. “As an advocate I want to dispel the myths about breast cancer.

It’s important to take the fear out of clinical trials and to tell the public about the importance of research.”

Jane Condon, manager of Patient Advocacy, coordinates the activities of the men and women who provide this critical patient perspective for researchers. Vanderbilt-Ingram is one of the only cancer centers in the country with a leader like Condon dedicated to managing a research advocacy program.

“Previously there wasn’t a defined role or a job description for research advocates, so now we’re developing those definitions,” Condon said. “The advocates decided as a group they wanted additional training, so for the past year they have been attending a series of scientific workshops and educational sessions to develop and enhance their skills. They are also writing a training manual to help future advocates understand their role in the research process.”

These activities have broadened the scope of the advocates’ activities within the Cancer Center and they are now being assigned to other research committees outside of the SPORE setting.

One of the goals of the advocacy program is to develop community education programs and materials to spread the word about cancer research and clinical trials to a wider audience. “Cancer research advocates have a unique opportunity to educate and engage the community in meaningful discussions about research,” Condon said.

– by Dagny Stuart



PHOTOS BY DEAN DIXON

From left, Drs. Carlos Arteaga, David Carbone, and Robert Coffey, who direct Specialized Programs of Research Excellence (SPOREs) in breast, lung and gastrointestinal cancers. Vanderbilt-Ingram is one of only seven cancer centers to hold three or more of these prestigious awards from the National Cancer Institute.

“The gap between what we understand about cancer and what we can do about cancer has significantly narrowed in the last 10 years.”



drug designed to interact with a specific protein that in essence drives the cancer. If you stop that protein you stop the cancer.”

Matrisian is one of the Vanderbilt-Ingram researchers devoted to advancing translational research so patients benefit more quickly from discoveries in the laboratory. She is now taking her expertise to Washington, D.C., where she has been appointed to a leadership post with the National Cancer Institute’s Translational Research Group. For the next two years she will spend half of her time at NCI headquarters, spearheading the effort to streamline the government’s oversight and funding of translational research.

Vanderbilt-Ingram now ranks seventh in the nation in research funding from the NCI, receiving 147 grants of more than \$66 million in fiscal year 2007. This includes three SPORE grants (in lung, breast and gastrointestinal cancer) and other “team science” grants designed to facilitate the interaction and collaboration required to make scientific translation happen more deliberately and more quickly. In fact, to be successfully funded, SPOREs must focus on translational research that links knowledge of human biology to develop and test interventions in patients.

“It is absolutely critical to have an environment in which a variety of individuals work well together as a team – basic researchers, physician-scientists and physicians who focus on patient,” said Jennifer Pietenpol, Ph.D., director of Vanderbilt-Ingram. “The SPOREs, for example, include investigators in 10 or 12 different academic departments and divisions, all bringing their perspective, knowledge and skills to bear. The growth in our funding is a tribute to our approach to team science and our focus on how we can impact patients.”

One focus of Pietenpol’s own NCI-funded research is to find biomarkers for a type of breast cancer whose causes remain a mystery. These so-called “triple negative” breast cancers are negative for estrogen and progesterone receptor expression and HER2 gene amplification. While they have a distinct gene expression profile, they do not

respond to commonly used chemotherapy drugs. Pietenpol, Ingrid Mayer, M.D., Josh Bauer, Ph.D., and Jennifer Rosenbluth are trying to find the clues that will tell them what is driving cancer growth in those tumors. If they can find those targets in the laboratory, they may be able to identify combinations of drugs or targeted therapies that can effectively stop or slow the cancer’s growth.

While the mechanisms for some types of cancer are still hidden in the maelstrom of human biology, researchers say the mist is beginning to clear and it’s happening quickly.

“It’s important for people to know that the gap between what we understand about cancer and what we can do about cancer has significantly narrowed in the last 10 years,” explained Robert Coffey Jr., M.D., professor of Cell and Developmental Biology and co-director of the Vanderbilt-Ingram GI SPORE grant from NCI. The GI SPORE is focused on colorectal cancer research. An estimated 153,760 patients were diagnosed with colon and rectal cancer in the United States in 2007 with 52,180 deaths, according to the NCI.

Coffey and GI SPORE co-director Mace Rothenberg, M.D., professor of Medicine, are utilizing the Vanderbilt imaging center to look at what happens to cells when they are hit with targeted agents.

“We have been able to non-invasively image cell proliferation, cell death or apoptosis and EGF receptor levels in mouse tumors, and we can do it in real time,” said Coffey. “We’re hoping to advance these imaging capabilities into human trials so we can determine whether a patient has responded to a treatment. This would eliminate the need for invasive tumor biopsies.”

Coffey says far too few patients are signing up for the clinical trials that could determine how well some of the new targeted agents work. Those clinical trials have helped accelerate the pace of translational research.

Patients play a pivotal role

After her experience in the Herceptin test, Teresa Lundberg has become an advocate for clinical trials.

“To this day, if there were a trial I was a candidate for, I’d be the first to raise my hand because I’ve seen so much good come from these trials,” she said.



Lundberg credits support from family and friends and the resources and support at the cancer center for her positive experience.

“The staff in the infusion room are walking angels,” said Lundberg. “Then there was Pam Carney, the clinical trials nurse who helped coordinate my care. Pam was absolutely my guardian angel because I didn’t have to worry about making appointments, when to get my blood work done and where I was supposed to be. She was my relaxing soul.”

Lundberg says she now recommends that other adults consider clinical trials.

Patients also contribute to scientific discovery when researchers are allowed to study tissue and blood samples obtained during biopsies and surgeries. As scientists develop new theories, it’s crucial for them to test those ideas by studying human samples to search for blood and tumor biomarkers.

Vanderbilt has created a massive DNA databank with as many as 50,000 DNA samples obtained from blood specimens by late 2008. The Ayers Institute for Pre-Cancer Detection and Diagnosis at Vanderbilt-Ingram is building another repository for colon polyps. Because colon polyps often become cancerous, this database of tissue samples is helping researchers gain insights into what causes polyps and whether they are likely to recur. One of the goals of the Ayers Institute is to create a blood test that would predict colon cancer.

A blood test to predict or confirm the presence of cancer is the scientific community’s magic quest. While researchers are moving forward on this quest, the prize has proved to be elusive. David Carbone, M.D., Ph.D., professor of Medicine and co-director of the Vanderbilt-Ingram Lung Cancer SPORE, is focused on developing such a blood test for lung cancer because it is the most common cancer

Teresa Lundberg, with Vern Steiner, gives a lot of credit for helping her through her cancer experience to family and friends. Behind them, trainer Alyssa Head and Goin’ for the Bucks.

without an approved screening and early detection test. Far too many lung cancer patients aren’t diagnosed until the disease is advanced, and this delayed diagnosis is just one of the reasons only 15 percent of people diagnosed with lung cancer are alive five years later.

“The most common imaging tests simply tell us there is something suspicious in one of the nodes in the lung,” explained Carbone. “We have to do an invasive test to find out if the tissue is cancerous. We believe there is a better way to get the answer by looking at proteins in the blood that could serve as biomarkers for lung cancer.”

This search for biological targets is the hallmark of today’s cancer research, and since each cancer patient’s biological signature is different, scientists say treatments are becoming much more individualized.

“The challenge is how to rationally combine multiple drugs for the right patient,” according to Carlos Arteaga. “We’re trying to determine how to predict, based on the genetic makeup of the tumor at the time of diagnosis, what would be the two or three combinations that would be rational for that patient and that will be well-tolerated and affordable. Those are big questions and the essence of personalized medicine. That’s a major frontier.” ●



Find out more about the NCI’s translational research working group and other initiatives by logging on at www.cancer.gov and entering “translational research” into the search box.



Navigating Cancer Care



From the very diagnosis, asking questions and seeking information is key to helping patients get the ‘right treatment for the right cancer’



When the doctor says “it’s cancer,” it’s not just the much-feared diagnosis itself that can affect the rest of your life. Right from the start, decisions about treatment can be key to fending off the nation’s second largest killer.

Today, many patients who receive appropriate care can expect to become cancer-free, while more and more are living with the disease much like any other chronic condition. Cancer care in the United States arguably is the best in the world; still, some patients suffer through misdiagnosis, substandard treatment and inadequate follow-up that can reduce their chances for the best outcome.

Diagnosis and treatment can vary widely, research suggests, leading to recommendations that patients and their advocates take proactive steps to ensure that the treatment recommended for their specific cancer reflects the current standards of best care.

By Elizabeth Older | Illustration by Nicholas Wilton





“I don’t want to give my patients a false sense of lack of urgency, but I think they need to understand that there is time to make a decision – and a thoughtful one,” says David Johnson, M.D., deputy director at the Vanderbilt-Ingram Cancer Center and former president of the American Society of Clinical Oncology (ASCO).

Stephen B. Edge, M.D., whose research looks at ways to evaluate and improve the quality of cancer care, says that there’s “no question many Americans do not get good cancer care. It is simply not a matter of debate anymore.”

The single biggest reason is lack of adequate health insurance, says Edge, medical director of the Breast Center at Roswell Park Cancer Institute in Buffalo, N.Y. That affects access to care and often costs patients an early-detection advantage because they delay going to the doctor or don’t get recommended cancer screenings.

“There are certainly these kinds of barriers to care, but our system is very chaotic,” Edge explains. “Coordination of care over time is essential. Cancer care extends over time and requires the input of four or five doctors.”

The gap in cancer care was highlighted in a 1999 report from the Institute of Medicine’s National Cancer Policy Board, which prompted several major initiatives aimed at measuring and improving the quality of cancer care.

In 2006, the first national study to assess the quality of cancer care showed that patients with early-stage breast cancer received 86 percent of generally recommended care, while patients with early-stage colorectal cancers received 78 percent of generally recommended care. Commissioned by ASCO, this research for the first time quantified the cancer care gap based on nearly 1,800 patient surveys and medical records in five major metropolitan areas. The study did indicate the quality of cancer care generally was better than that for some other common diseases, such as hypertension and diabetes, but more analysis will be needed to learn why care differed, in some cases dramatically, says Johnson, Cornelius Abernathy Craig Professor of Medical and Surgical Oncology.

“This is a treasure trove of data,” Johnson says.

In the meantime, experts say, patients should arm themselves with information as they navigate their way to the cancer care decisions that are best for them.

➤ The importance of a second opinion

If a cancer diagnosis happens to come from an experienced cancer specialist with top-notch credentials, a patient may not feel the need to get a second opinion before beginning treatment. However, with a potentially life-threatening disease like cancer, most doctors expect – in fact, some even encourage – patients to seek advice from another physician.

“They have to depend on their doctor,” says Johnson. “I think with cancer, you have to assume a doctor who is board certified is, in fact, a capable individual. However, I think it’s quite appropriate to get a second opinion.” Even so, insurance coverage for second opinions varies by policy and type of treatment, so in some circumstances patients may face paying for this reassuring step.

The first goal in the second-opinion process should be to confirm the diagnosis (see story on p. 33). At Vanderbilt-Ingram, all reports and pathology slides are reviewed when a patient comes for a consultation, and additional tests are done if necessary. This intense evaluation is important because all cancers are not alike. A doctor who routinely treats just one or a few types of cancer may use specialized knowledge and diagnostic tests to evaluate the type and extent of a cancer – called staging – which is imperative to getting the most appropriate treatment at the start of care.



While the Internet and other sources have made it possible for patients to learn a lot about their disease, ultimately they will need to rely on a trusted medical professional to help them evaluate that information, says Johnson.

“What most patients want is guidance,” he says.

➤ Seek out experienced physicians and facilities

All board-certified oncologists should have the same basic credentials. However, specialized centers, particularly those associated with universities, have experts who focus on specific cancers and benefit from access to world-class research and technology.

“It’s volume and specialization; it’s a multidisciplinary team approach that distinguishes academic-based centers,” Johnson says. “The culture at a teaching institution like Vanderbilt is such that every decision is questioned and reviewed by one’s peers very, very thoroughly, so what emerges is a very appropriate plan for each patient.”

While these are not the only factors that affect outcome, survival statistics for patients treated at major cancer centers for certain malignancies exceed those of people treated by less specialized doctors and facilities, Johnson points out. Doctors who treat just one or a few specific cancers statistically are better at it, and those who specialize in rare or aggressive cancers may have unique expertise.

“Patients generally can understand how experience relates to outcomes,” says Joseph A. Smith, M.D. “In particular, urologic cancer outcomes are directly related to the training and expertise of the surgeon.”

PHOTO BY DEAN DIXON



David Johnson, M.D., a lung cancer specialist and cancer survivor, says he is optimistic that cancer care will get better and more consistent in the years ahead – but that improvement will take time.



Questions you should ask as you choose a doctor

- 1 | Does this doctor or surgeon have the education and training to meet my needs?
- 2 | Does this doctor or surgeon work as part of a multi-disciplinary team that specializes in my type of cancer?
- 3 | Does this doctor or surgeon see patients at the treatment facility I've chosen?
- 4 | Is the doctor board-certified, and if so, in what specialties?
- 5 | Has this doctor been evaluated by a professional society such as the American College of Surgeons?
- 6 | What types of cancer does this doctor or surgeon treat?
- 7 | How many patients with my type of cancer does this doctor or surgeon treat?
- 8 | How often does this surgeon perform the type of surgery that I need? What are his or her success rates?
- 9 | Is this doctor or surgeon involved in research and clinical trials?
- 10 | What new technologies or surgical procedures does this doctor or surgeon offer?
- 11 | Who covers for this doctor or surgeon when he or she is away? Does this person have access to my records?
- 12 | How long does it take to get an appointment with this doctor or surgeon?
- 13 | Does this doctor or surgeon listen to me and treat me with respect?
- 14 | Does this doctor or surgeon explain things clearly?
- 15 | Who else is on the treatment team? What are their qualifications and expertise?
- 16 | Is this doctor covered by my health plan?

Smith chairs Vanderbilt's Department of Urologic Surgery, which is ranked among the nation's best in this specialty by *U.S. News and World Report* and includes physicians who are nationally recognized experts in a variety of urologic cancers. The department also has been a leader in robotic and minimally invasive surgical procedures.

Vanderbilt's urologic oncologists see patients referred by urologists in the community, as well as family physicians. That number includes many patients with prostate cancer, for whom treatment recommendations can be diverse and confusing.

While it isn't common for a patient to get a different diagnosis at Vanderbilt, it's not unusual for treatment recommendations to differ, especially when combined regimens are considered, Smith says.

"Selecting the right treatment for the right cancer is key," he says.

Joe B. Putnam Jr., M.D., deals with many cancers that don't come with a lot of good treatment options. Well-meaning doctors sometimes rush patients into treatment when time might be better spent carefully diagnosing the stage of the cancer, determining the best treatment sequence and considering other factors, explains Putnam, Vanderbilt's chairman of Thoracic Surgery.

"You need to make the best decision possible the first time," says Putnam, an Ingram Professor of Surgery who routinely treats cancers of the chest, including those of the lung and esophagus.

As cancer specialists do throughout Vanderbilt-Ingram, Putnam gets input on individual cases from a multidisciplinary team of physicians, as well as other specialists as needed.

"With that, you have multiple perspectives, multiple therapies available," he explains, the coordination of which has become integral to cancer care as patient treatment plans often include more than one approach. "I think we do multidisciplinary care here at Vanderbilt probably at a world-class level."

Both Smith and Putnam point to the importance of highly skilled nurses and other medical staff, as well as up-to-the-minute technology, as imperative for delivering quality cancer care for every patient.

"If you do something over and over, you tend to get very good at it, very efficient," says Putnam. That combination can drive down costs while also giving patients more statistical confidence about the care they will receive, he says.

Vanderbilt physicians are accustomed to providing both initial treatment consultations and second opinions, and they understand that many patients will want to know if they can have their treatment just as well close to home.

"Having the appropriate care as close as possible to the family's home is highly desirable," says Putnam.

Most patients who come for consultations at Vanderbilt should be able to return to their home community to get their treatment, Johnson says. But, he adds, research suggests that certain cancers – even common, highly curable ones – may be more successfully treated at major cancer centers.

➤ Guidelines emerge to help doctors and patients

The managed care movement that emerged in the 1970s brought with it efforts to better define what tests and treatments were proven effective for specific conditions. While there have been drawbacks associated with managed care, the movement did usher in a growing focus on evidence-based medicine, the concept that best practices can be defined by looking to research results and, in some cases, expert consensus.

Cancer doctors and their patients have some very specific guidelines to consult when considering treatments and timelines. The National Comprehensive Cancer Network (NCCN), a consortium of 21 of the world's premier cancer centers including Vanderbilt-Ingram, has developed free Web resources for both clinicians and patients. The guidelines detail best-practice treatments for the cancers that affect 95 percent of all patients.

"We hope it will end up with better care for patients, and I think it will," says Joan S. McClure, M.S., who is responsible for the

Selecting the right treatment for the right cancer is key.



PHOTO BY ANNE RAYNER



PHOTO BY ANNE RAYNER



NCCN guidelines as the network's senior vice president of clinical information and publications.

Other diagnosis and treatment information is available from the NCI, the American College of Surgeons and ASCO.

NCCN's guidelines are developed and regularly updated by panels of different specialists from the 21 member centers. This multi-disciplinary approach aids in the coordination of care from one cancer specialist to another, McClure said, noting that treatment "decision trees" may apply to as many as 85 percent of patients.

"In every practice there are going to be patients who don't fit the guidelines," she explains. "If a practitioner is slavishly following the guidelines regardless of the situation, that would not represent good quality care."

The biggest barrier to defining quality cancer care may be that people have trouble pinpointing what to measure, Johnson explains.

Left, Joseph Smith, M.D., performs robotic prostate cancer surgery. Vanderbilt has become a leading center for this procedure. See a demonstration at www.orlive.com/vanderbilt/1227. Right, Joe B. (Bill) Putnam, M.D., leads a thoracic surgical team that focuses on surgical treatment of malignant and benign diseases of the chest. More info at www.vicc.org/videos/lung.



Questions you should ask as you choose a cancer center or hospital

- 1 | How many cancer patients does this center treat?
- 2 | Does this center specialize in my type of cancer?
- 3 | Does this center have teams of specialists in specific types of cancer who meet regularly to discuss cases (called tumor boards or conferences)?
- 4 | If so, how specialized are these teams? What types of specialists are involved in these meetings?
- 5 | Does the center or hospital conduct research and does it offer clinical trials for my cancer?
- 6 | What support services does this center provide?
- 7 | How will this center support my quality of life during and after treatment?
- 8 | Is the center designated by the National Cancer Institute?
- 9 | Is the center approved by the American College of Surgeons' Commission on Cancer?
- 10 | Is the center accredited by the Joint Commission on Accreditation of Healthcare Organizations?
- 11 | Is this center part of a Magnet hospital recognized for quality nursing care?
- 12 | What new or innovative technologies or procedures does this center offer?
- 13 | Is this center covered by my health plan?
- 14 | Is the center a part of the National Comprehensive Cancer Network?
- 15 | How does the facility check on and work to improve its quality of care?
- 16 | Does the facility explain patients' rights and responsibilities? Are copies of this information available to patients?

While some want to focus on process measures – what is done and when it is done – others suggest that patient outcomes – how people fare after treatment – ultimately are most important.

“It’s a very big and challenging problem” for which gathering evidence is both time-consuming and costly, he says.

For patients, the availability of guidelines can be a source of comfort as they consult with doctors about their own specific diagnosis and treatment options. Ultimately, though, those guidelines must be taken into account with other factors, and the best care will be individualized, Putnam says. “We take care of patients one at a time,” he says. “I tell patients that together we will make a good decision – we will make the best decision for you.”

➤ Look for survivor support

With more than 10 million Americans living today with a history of cancer, it’s clear the disease is an everyday factor in the lives of many people. However, providing ongoing monitoring and follow-up care for these patients is a relatively new and growing challenge for the medical community.

“We know that people who have had cancer are at risk for other disease processes,” not only a recurrence of cancer, but also other problems caused by cancer treatments, explains Johnson.

Vanderbilt-Ingram provides support through a comprehensive survivorship clinic and through patient education and outreach programs, including partnership with programs including the American Cancer Society and Gilda’s Club Nashville. But Johnson says the hope is that physicians in training today will learn more about how to provide proper monitoring and follow-up care for survivors, especially as their numbers are expected to balloon as the oversized baby-boom generation moves into old age, when cancer becomes more common.

“We definitely provide this at Vanderbilt, but our view is this should not be a service that is unique to us,” Johnson says. “It’s a good problem (caring for long-term survivors), in a bizarre sort of way.”

Recognizing the challenges facing cancer survivors, several medical sources have developed in-depth information and guidance. These include ASCO’s People Living with Cancer Web site, www.plwc.org, and the NCI’s cancer survivorship Web pages, www.survivorship.cancer.gov.

As for the future of the quality of cancer care in America, Johnson says he’s optimistic that over time it will get better and more consistent for all those who need it.

“However, I think it will be evolutionary, not revolutionary,” he observes. “It’s going to take time.” ●



Vanderbilt-Ingram has created a Web site to help patients navigate their cancer choices at www.vicc.org/choose.

The Power of a Second Opinion

Jim Grant is living proof that not every cancer diagnosis should be taken as the final word.

When doctors in Hopkinsville, Ky., told Jim he had lung cancer and needed immediate surgery, he and his wife, Brigitte, decided to get a second opinion at Vanderbilt-Ingram Cancer Center, one of only 39 National Cancer Institute-designated Comprehensive Cancer Centers.

Brigitte, whose first husband died of lung cancer, wondered if the newly diagnosed malignancy could be related to the bladder cancer Jim had been treated for a year earlier, but the local specialist assured her that it wasn't.

The family physician helped get Jim an appointment at Vanderbilt-Ingram, but desperate to see a doctor sooner, Brigitte went online and filled out the self-referral form on the center's Web site. Within hours, she was talking to a nurse with the Cancer Information Program.

Started in 1997, the toll-free telephone resource now has four nurses who field some 3,000 calls each year, says program director Teresa Knoop, R.N., who holds a master's degree in nursing and has more than 20 years experience. People call to locate a doctor skilled in a specific procedure, arrange for a second opinion and, most often, to find out about innovative investigational treatments offered through clinical trials.

The nurses help patients work through insurance issues, pull together medical records and cross other hurdles, often logging dozens of phone calls and e-mails for a single caller. Knoop has found that people may not realize the difference a second opinion can make, while many

older patients, especially, feel they will offend their hometown physician by asking about it.

"They don't know to get a second opinion," she says. "They don't understand the importance of that, or they're just absolutely scared." But she knows from experience that the vast majority of oncologists and other physicians are very supportive when patients decide to ask another doctor to review their case. "Every day, I see it can make a difference," she says.

As for Brigitte's experience, she has high praise for the nurses and the assistance they offer patients and their family members.

"I think I called every day to see if there was a cancellation," she says, mentioning nurse Pam Carney as a frequent contact. Her persistence paid off. Vanderbilt lung cancer specialist David Carbone, M.D., Ph.D., stayed late one day just after Thanksgiving to meet with the Grants and the second opinion process was set in motion.

Within a few days Carbone called with a message: "I've got good news. It's bladder cancer, not lung cancer," Brigitte recalls. A review of Jim's case had revealed that the tumor in the lung was bladder cancer that had spread, which meant the

treatment would be different and the prognosis was much more promising. Jim began the first of four monthly treatments in December.

The 64-year-old health enthusiast has this advice for people faced with a cancer diagnosis: "I think if you're at a community hospital where they're not as specialized, you definitely need a second opinion." While acknowledging that patients naturally might want to avoid the cost and time required to travel to a dedicated cancer center, Jim continues, "In the long run, it's something you really need to do. It's too serious a thing to take the easy way out."

The tenacious Brigitte agrees: "Absolutely, go talk to another physician, a specialized oncologist in the particular field. The diagnosis could be the same, but you have the peace of mind of knowing that it is." — by Elizabeth Older



PHOTO BY NEIL BRAKE



THOMAS YANKEELOV, PH.D.



CANCER

An Inside View

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IMAGING LURES THE ENEMY OUT OF THE SHADOWS

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For most of human history, cancer remained largely hidden from view. Unless the tumor could be felt (breast cancer) or seen (skin cancer), this imperceptible intruder lurked quietly inside the body until its spread ultimately led to the death of the patient.

With the discovery of radiation and X-rays in the late 1800s, cancer began to come out of the shadows. For more than 50 years, X-rays remained one of the only noninvasive ways to see inside the body.

Today there are many ways to track down this hidden killer, including X-ray, CT, MRI, ultrasound, and nuclear medicine modalities like PET.

By Melissa Marino | Photograph by Dean Dixon



• While these • imaging methods • are indispensable

to cancer diagnosis, treatment and follow-up, making true progress against this disease will require more refined, detailed views of cancer. Researchers in the Vanderbilt-Ingram Cancer Center and Vanderbilt University Institute of Imaging Science (VUIIS) are working together to develop more sensitive and informative imaging technologies that not only provide the location and size of tumors, but reveal the inner biology and behavior of cancer.

Sizing up cancer imaging • • • • •

Imaging plays an integral role at all stages of cancer care.

“We use imaging for cancer in a few different settings,” says Dennis Hallahan, M.D., Ingram Professor of Cancer Research and professor and chair of Radiation Oncology at Vanderbilt-Ingram Cancer Center.

One of the most common uses for imaging is in screening for cancer, for example, traditional mammography screening for breast cancer. When cancer is suspected, imaging is used to find where the cancer is located in the body.

Beyond diagnosis, imaging plays an important role in determining how advanced the disease is. This process, called staging, Hallahan explains, “tells us the best way to manage the disease. For example, if a patient has metastatic disease, they’re probably not going to undergo surgery.”

Imaging can also help physicians and researchers evaluate a patient’s response to therapy and monitor for cancer recurrence. This use is particularly important for measuring the effectiveness of new therapeutics.

While standard imaging modalities have been central to improving diagnosis and cancer care, the measurements they give are crude estimates of cancer response.

“Historically, the things imaging is used for...are all based on morphology – sizes and shapes and volumes of the tumor,” says Thomas Yankeelov, Ph.D., Cancer Center member and director of Cancer Imaging at VUIIS. To monitor tumor response to therapy, for example, the size of the tumor after treatment is compared to tumor size before treatment based on a CT or MRI scan. But these measurements are only recorded for the two longest dimensions.

“That’s very limiting because every object in the known universe has three dimensions,” he says. “You can imagine, if (the tumor) is shifting, you may not even necessarily be measuring the same two dimensions before and after treatment.”

Yankeelov notes that only recently has the refinement of existing technologies – like CT and MRI – made it possible to obtain 3-D

views of tumors and to determine their volume, a better indicator of long-term response than the “longest dimension” criteria.

Using these criteria, changes in tumor size can usually only be detected after several weeks or months of treatment – a delay that can waste valuable time on ineffective treatments. Since the earliest responses to a cancer treatment occur on a much smaller (cellular) scale, the next generation of imaging methods will have to move beyond these rough physical parameters and probe the invisible realm – the biology of the tumor.

“What we’re trying to do now is to figure out what are the next generation of imaging devices and how should they be used in the clinic,” says Yankeelov. “We’re trying to be more quantitative in characterizing tumors. Instead of just measuring the tumor’s longest dimension, we want to know the volume, the tumor’s metabolic rate, the blood flow, hypoxia distribution, etc.”

Some of these features can be determined invasively with biopsies, says Yankeelov. But repeated biopsies are not practical in the clinic, and biopsies, by their nature, sample only a small portion of the tumor.

“We want to figure out how we can make those measurements with imaging, so that we can do it longitudinally and over time without having to cut into people,” Yankeelov says. Bringing these methods into the clinic for use in humans, however, first requires thorough studies in animals.

Animal models of cancer – especially genetically engineered mice – are central to bringing new imaging techniques to the clinic.

The VUIIS recently received a five-year, \$2.2 million grant from the National Cancer Institute (NCI) to apply new imaging techniques for studying cancer in small laboratory animals. This funding helped establish VUIIS as one of only 12 Centers for Small Animal Imaging in the nation.

The center houses scaled-down and more refined versions of all of the major medical imaging devices – including CT, MRI, PET, SPECT and ultrasound. Some other imaging methods, like optical imaging, are so far used mostly in preclinical (animal) research, with a few specialized clinical applications.

“All of them have a lot more flexibility than what you might find in the clinic,” says Yankeelov. And they all provide different information about the tumor.

“There’s no one imaging method that will answer all questions – they all have different strengths and weaknesses.”

Researchers often use different combinations of imaging methods to study cancer. But matching up the data from one imaging method to data from another is a major technical obstacle. To facilitate this process for use in small animal research, VUIIS members, whose expertise range from biology to physics and mathematics, have been developing procedures to help facilitate this process, called “registration.”

Yankeelov, a mathematician by training, is building mathematical models that synthesize data from multiple modalities, “so that you can truly have a comprehensive imaging characterization of tumor response.”

The problem of registration can be overcome by combining two different imaging modalities into a single apparatus. This allows

researchers to simultaneously obtain a tumor's physical measurements as well as information about the molecular processes going on in the tumor. Already, combined imaging is making an impact on cancer diagnosis and treatment in humans.

"Combined imaging is going to be big," says John Gore, Ph.D., director of the VUIIS and Cancer Center member. "These hybrid instruments will be able to give you information simultaneously. You'll be able to get physiological measurements, anatomical measurements, as well as molecular imaging information."

For example, PET-CT, which is already in clinical use, has been one of the great advances in cancer imaging. The PET scan detects glucose metabolism, which tells the physician whether a growth within the body is cancerous or not (malignant growths metabolize more glucose than benign tumors). CT provides detailed information about the size, shape and location of the tumor but cannot differentiate malignant lesions from normal or benign lesions as accurately as PET. Gore predicts that more types of combination imaging are on the horizon from MRI-PET to SPECT-CT.

Vanderbilt researchers are continuing to refine the existing platform of MRI for cancer monitoring. One advancement, called dynamic contrast-enhanced MRI (DCE-MRI), is already being tested in women to determine the effectiveness of targeted therapies in shrinking breast tumors.

DCE-MRI is a "general technique to look at blood flow and vessel permeability in tumors," explains Yankeelov, who conducted his graduate studies on the technology. "It's well known that a tumor can't survive on its own after it gets to be about a cubic millimeter. It has to vascularize (grow new blood vessels), in this well-known process called angiogenesis."

"Angiogenesis inhibitors" make up a large segment of recently developed targeted therapies, but their clinical effectiveness needs to be monitored over the long-term. DCE-MRI may be a way to observe if these drugs – which include Avastin and Sutent – are having their intended effect of preventing angiogenesis.

Vessel development inside a tumor is "very chaotic," says Yankeelov. These vessels are not normal – they are leaky and unstructured. "DCE-MRI is a way to probe that leakiness to see how tumors respond to these anti-angiogenesis drugs, and do it non-invasively over time," he says. "It's a very useful tool. But it's not a magic tool that tells you everything you need to know about a tumor." It will, he says, need to be combined with other measures of cellular proliferation and other molecular features of the tumor.

Going molecular ■ ■ ■ ■ ■ ■ ■ ■ ■ ■

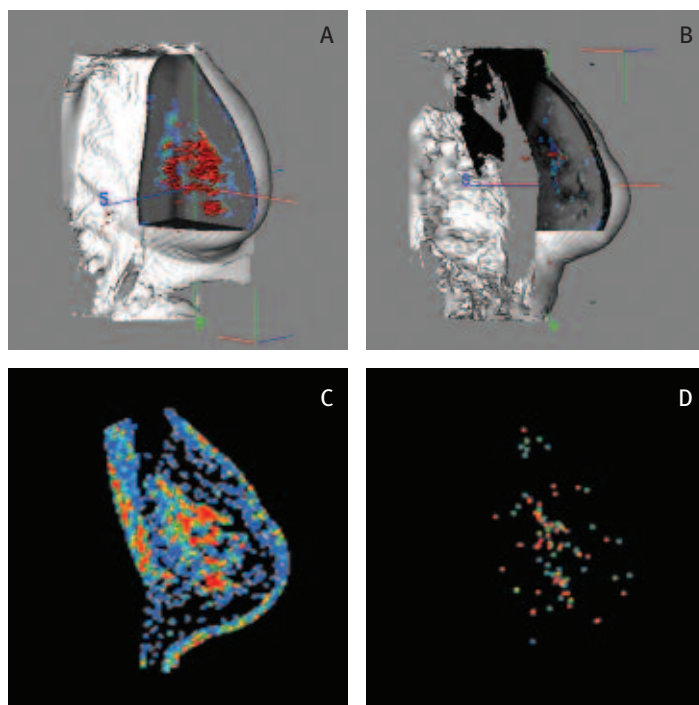
Molecular imaging, or imaging based on advancements in basic molecular and cellular biology and genetics, is one of the most exciting and promising new avenues for imaging.

VUIIS and Cancer Center scientists are working to develop novel molecular imaging methods, including molecular probes that can reveal aspects of tumor behavior.

PICTURED HERE: Fragile, leaky blood vessels nourishing a breast tumor are revealed with the help of dynamic contrast-enhanced MRI. The red voxels (three-dimensional data points) produce a 3-D volume rendering of blood flow (perfusion) and leakiness (permeability) before treatment (A).

In the same patient after chemotherapy (B), a drastic reduction in perfusion/permeability indicates treatment is successfully "starving" the tumor by disrupting its blood supply.

(C) and (D) are single-slice images taken from the center of the 3-D volume renderings before and after treatment. The hope is that this kind of analysis will enable doctors to determine early on whether the tumor is responding to therapy.



"Part of the thrust in cancer imaging now is, can you target treatment knowing more about the tumor?" says Gore. "Characterizing the tumor more completely is important especially for first-line medicine. And that's one thing that imaging will be able to do quite well."

Molecular, functional and metabolic imaging has the potential to reveal physiologic, cellular and molecular processes related to disease. These include glucose metabolism, blood flow, oxygen use, cell proliferation rate, and alterations in gene expression and intracellular signaling pathways that influence tumor behavior.

Such techniques may find uses in early diagnosis by detecting changes happening at the cellular or molecular level that appear before the onset of symptoms.



Dennis Hallahan, M.D., adjusts a plastic frame that holds the head still during treatment using an image-guided radiation therapy (IGRT) system. Using this IGRT system, doctors at Vanderbilt are able to treat cancers with much greater precision, including offering “gating,” which coordinates the delivery of radiation with the movement of the body during breathing.

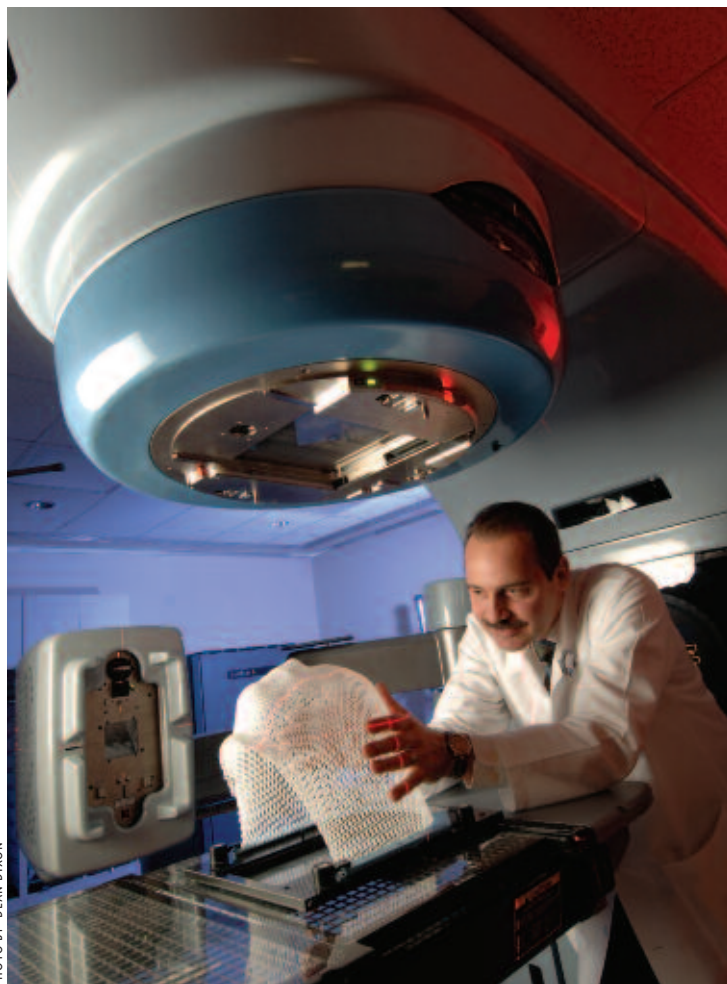


PHOTO BY DEAN DIXON

Recently, Cancer Center member Robert Coffey, M.D., and Vanderbilt chemistry professor Darryl Bornhop, Ph.D., reported their development of novel fluorescent ligands of the peripheral benzodiazepine receptor (PBR), a membrane protein whose expression is increased in colon, prostate and breast cancer. Using this ligand, which was tagged with a fluorescent (light-emitting) compound, the researchers were able to detect early stage colon tumors in mice genetically predisposed to developing colon cancer. The probe also accurately distinguished the tumors from inflammation – key to developing a sensitive and specific screening test for cancer.

“The ability to follow molecular events *in vivo* represents a paradigm shift for medical science,” they wrote in their April 2007 paper reporting these results. “A critically important goal of molecular imaging studies is to detect spontaneously arising tumors in the context of the host/tumor microenvironment.”

This particular molecular imaging tool will facilitate rapid cancer screening in animal models. But the researchers are also working to adapt the technology for human use by labeling the probes with radioactive compounds for use in existing clinical platforms, like

SPECT and PET, with the long-term goal of improving the early diagnosis and therapy monitoring in colon cancer.

“Additionally,” they wrote, “we expect these agents to be useful for noninvasive monitoring of therapeutic efficacy that should be useful in improving clinical outcomes.”

Molecular-based imaging may also allow physicians to determine, based on the tumor’s molecular characteristics, which targeted treatments would be most likely to work in a particular patient.

For example, Gore asks, “why take an agent targeting estrogen receptors if the tumor doesn’t have estrogen receptors?”

With molecular imaging, one could potentially “tag” probes that bind to particular receptors to see if a patient’s tumor expresses those receptors, and thus be likely to respond to drugs targeted to those receptors.

Perhaps the most promising application of molecular cancer imaging will be monitoring cancer response to therapy. These new methods are now possible because of advancements in understanding the biology of cancer.

“The big push in the last few years has been to develop better methods for assessing whether drugs are hitting their targets, and judging whether patients are doing well,” says Gore. “Our understanding of cancer biology will help us develop biomarkers of cancer response to treatment.”

Already, several Vanderbilt researchers are making progress in this area.

In November 2007, a multidisciplinary team of investigators including Gore, Hallahan, and Andrej Lyshchik, M.D., Ph.D., a Radiology resident, reported that “molecular ultrasonography” – ultrasound technology targeted to specific molecules – may enable *in vivo* imaging of biomarkers in tumor blood vessels, which could be used to evaluate early tumor responses to anti-angiogenic drugs.

In a mouse breast cancer model, they investigated the use of high-frequency ultrasound coupled with a contrast agent targeted to the vascular endothelial growth factor receptor 2 (VEGFR2), a receptor that is highly expressed in new tumor blood vessels and is a major target for several angiogenesis inhibitors.

They showed that the intensity of the ultrasound signal in the tumors correlated with the expression of VEGFR2, as confirmed by immunoblotting and histologic evaluation.

This technology, contrast-enhanced high-frequency ultrasonography, they wrote, “has several important advantages over other molecular modalities for *in vivo* imaging of angiogenesis.” It is portable, readily available, and is the only imaging modality that can provide real-time imaging. Ultrasound also is generally less expensive than nuclear imaging and MRI.

In addition to adapting technologies for molecular imaging, Vanderbilt researchers are also identifying novel molecular probes that may help individualize cancer treatments and speed up development of new cancer therapies.

Hallahan and colleagues recently developed a technique that may be able to determine a cancer treatment’s effectiveness

within days of starting treatment instead of the weeks or months it currently takes.

“It currently takes two to three months of cancer therapy before we can determine whether the therapy has been effective for a patient,” says Hallahan. “If we can get that answer within one to two days, we can switch that patient to an alternative regimen very quickly.”

From a panel of billions of protein fragments, or peptides, Hallahan and colleagues identified one that specifically bound to tumors dying in response to a targeted therapy. To this peptide, they attached a light-emitting molecule and injected these labeled peptides into mice that had been implanted with human tumors.

Using specialized imaging cameras that detect light in the near-infrared range (invisible to the human eye), the investigators saw that tumors responding to therapy were “brighter” than non-responding tumors. The peptide detected response in a wide range of tumors – brain, lung, colon, prostate and breast – within two days of initiating treatment.

“The key word here is ‘days,’” Hallahan says. “This will allow us to minimize the duration of treatments with ineffective regimens in cancer patients.”

The next step will be to move the technology into humans. The imaging technique used in mice (near-infrared) is not sensitive enough to penetrate deeply into human tissues, so the researchers are adapting the technology to an imaging modality commonly used in humans, like PET.

Hallahan predicts that the peptide may enter clinical trials within 18 months. If the probe works as well in humans as it does in mice, he says, such molecular imaging methods could help accelerate the development of new chemotherapeutic drugs.

“In the pharmaceutical industry, we’ll have a patient on a drug for months before we can re-evaluate the size of the tumor,” Hallahan said. “If we can get that answer within a couple of days, it will speed cancer drug development in the early phases of clinical trials.”

This new frontier of molecular imaging holds much promise, but also faces major obstacles – not the least of which is funding.

“Funding is a real problem,” Hallahan notes. Federal sources of funding focus primarily on discovery research, but support for translating these discoveries into humans is scarce. Commercial interest is also limited since each kind of test may only be applicable in a small number of patients.

“There’s really a minimal amount of funding for that,” he says. “We have to make that road a little easier from discovery to application.”

Despite the roadblocks, Vanderbilt researchers will keep pursuing new avenues for viewing cancer’s march through the body.

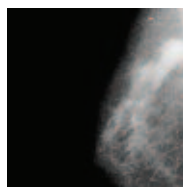
“Imaging is a very useful tool,” Gore says. “You know exactly where you’re looking, how big it is. Imaging has a really persuasive message.”



web link

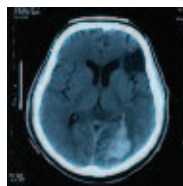
Find out more about Vanderbilt’s Institute for Imaging Science at www.vuii.vanderbilt.edu.

COMMON CANCER IMAGING MODALITIES



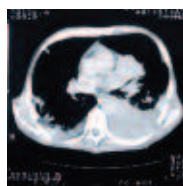
X-ray imaging (radiography)

Short pulses of radiation (X-rays) are shot through a body with a photographic or digital film behind. As the X-rays hit the film, it turns from white to black, leaving a pattern of bright (where few X-rays hit) and dark (where many X-rays hit) on the film. Different tissues within the body absorb the X-rays to varying degrees, resulting in the contrast seen in an X-ray image.



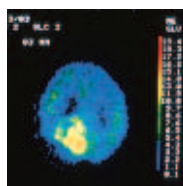
CT (computed tomography) or CAT (computed axial tomography)

The fundamental limitation of X-ray radiography is that it generates 2-D images of 3-D objects. The CT scanner eliminates this problem by taking a series of 2-dimensional X-ray “slices” through the body from many angles and a computer uses these 2-D to generate a 3-D view.



MRI (magnetic resonance imaging)

MRI forms images of inside the body by exposing the patient to changing magnetic fields, which cause water molecules in the body to absorb and give off energy. The scanner first sends in radio waves and then measures those given off by the tissues. Different tissues give off radio waves in different ways, generating the contrast seen in an image. MRI can reveal exquisite soft tissue details, and does not expose patients to potentially harmful radiation.



Nuclear imaging techniques: PET (positron emission tomography) and SPECT (single photon emission computed tomography)

PET and SPECT scans utilize radioactively labeled compounds (tracers) to obtain information about the biology of body tissues. In the most common use of PET, a radioactive sugar is taken up and metabolized more readily by tumor cells (since cancer cells burn more energy than healthy cells), distinguishing a cancerous tissue from its normal surroundings.



Ultrasound (US)

Ultrasound techniques direct high-frequency sound waves into the body, which, upon hitting tissues, are reflected back to a detector. A computer then creates an image of the tissue. Ultrasound can’t penetrate deeply into the body, but has become essential for visualizing tumors in tissues that lie just under the skin (e.g., breast and thyroid).



STORIES OF SURVIVAL

PAM MARTIN

In Her Own Words





Photo by Dana Johnson

“Life is like a box of chocolates. You never know what you’re gonna get.” – Forrest Gump

I sure didn’t know what to expect when I got a cancer diagnosis. I was 33, the mother of two small children, no family history of cancer, no known risk factors. I was healthy – I hardly ever got a cold. My husband, David, and I sat in the oncologist’s office dazed, hearing strange words like lumpectomy, mastectomy, lymph node dissection, node positive, node negative, ER-PR status, chemotherapy, radiation ... chances of survival. It was like getting hit by a truck, a Big Cancer Truck. We came home with handfuls of cancer brochures but no idea what was ahead. We stayed awake all night. We cried – a lot. That was April 1991.

Having cancer is personally a very lonely place; you experience a lot of losses physically, mentally, spiritually, and many times financially. There is a ripple effect to everyone you know. Your friends and family are devastated and feel totally helpless.

I had no frame of reference for anything that was happening. The treatment plan was surgery, chemo, radiation and then five years of tamoxifen. I took a gung-ho approach. I had chemo every third Friday, threw up all weekend, and was back at work on Monday. I was what you might call a “closet cancer patient;” no one knew I had cancer unless they had a reason to know. Before I lost my hair I went to a wig shop and got a perfect match for my shoulder-length hair. My hair started falling out on a Friday, I wore that wig on Monday, put mascara on the two eyelashes I had left and headed off to work. I scheduled my radiation for the late afternoon so I could go after work. Some days I was so tired that I didn’t feel like I could press the



Top left, Pam with her daughter, Sara Martin, and mother, Sara Owen, at the 2007 Susan G. Komen Nashville affiliate's Race for the Cure. Pam designed the Vanderbilt (V-Team) T-shirt. **Top Right**, Pam with inspiration Gail Addlestone (center) and Lynn Dunavant at the Country Music Marathon, which they walked to raise money and awareness for Gilda's Club Nashville. **Right**, Pam (center, with glasses) and a group of Nashville breast cancer survivors on an advocacy training and lobbying trip to Washington, D.C. **Below**, Pam and husband, David, during her treatment.



gas pedal – I thought I might have to use the cruise control just to drive home. But if anyone asked me how I was, I always said “great, really good, how are you?” I thought that if I said it enough, maybe it would be true. I remember going to my son’s baseball games in the hot midday sun with that wig on and about to have heat stroke. But I was doing just fine!

“Crazy Closet Cancer Patient” Finds Help

Sometimes I thought I really didn’t have cancer. You know, someone had mixed up my lab work. I was just taking the chemo to make everyone else happy. Well, I was really disturbed by these thoughts. I began to conclude that not only did I have cancer but that I was also crazy! I knew I needed help.

That help came from a support group that met in the hospital lobby. The people there were of different genders, ages, races and social standing. The one thing we had in common was that we all had cancer. We immediately bonded and understood each other in a powerful way that is hard to explain. That’s where I heard about a two-and-a-half day retreat for cancer patients called Camp Bluebird. My friend Kathy and I signed up with the contingency plan that we would meet my brother at the end of the road to pick us up if we didn’t like it. Well, that experience turned out to be the best medicine of all. I got



the chance to feel the things I needed to feel and a safe place to talk without having to put on a “happy face” for anyone. I cried until my eyes hurt. I laughed until my mouth was sore. I met people who had been through a cancer diagnosis and come out the other side. They were LIVING, regardless of their diagnosis. Their stories gave me so much hope. If they recovered, maybe I could, too.

Big Cancer Truck Strikes Again

David was on active duty in the Army during this time. When he was reassigned, I was nervous about leaving my support group and doctors. But I was feeling very healthy and my follow-up visits had been extended to every six months, so I was pretty confident that the cancer was gone for good. But during one of those follow-up appointments – January 1993, just 14 months after finishing my initial treatment – the Big Cancer Truck struck again. BAM! I had tumors in my chest, one pressing on my aorta. We were shocked because I didn’t look or feel sick. When they did the surgery and couldn’t get it all, I had to find new doctors near our new home. I was facing treatment again, and this time the prognosis was “very poor,” “extremely dismal.” With standard treatment, I might get a one-year remission. With a new experimental, radical treatment, I might get a “long-term” remission – maybe three years. Well, at 35 with children only 7 and 11, three years didn’t sound like “long-term” to me. But that’s what we were facing.

My treatment was to be high-dose chemotherapy, followed by a stem cell transplant of my own cells (called an autologous transplant). It was a very intense treatment that is sometimes called “stem cell rescue.” The high dose chemotherapy takes you to death’s door, wiping out the bone marrow along with – it was hoped – any cancer cells. Then you are “rescued” by the infusion of stem cells that rebuild the marrow. I was hospitalized several times and received blood and platelet transfusions. (THANK YOU to everyone who donates blood and platelets!) The day I got my cells back I went into an isolation room in the hospital. During this time I was very sick, I don’t remember the first few days. I couldn’t eat or even swallow a drop of water; I was fed intravenously. I lost all of my hair, my skin peeled, my nails came off. Now I can joke about it and call it my “Memphis Makeover” – it was like getting a chemical peel from the inside out! As soon as my bone marrow began to respond, it was like the lights came on, like waking up from a nightmare. I left the hospital and slowly continued to get better each day.

A blessing of time

It has now been 16 years since I first heard the words “you have cancer.” Time is one blessing that I have received, but that too many of my friends didn’t get.

When I was sick, I made up my mind that if got better I would try to make a difference for someone else with cancer. I knew I did not have what it takes to be a nurse (my all-time heroes), so I looked

Lessons learned along the way

You can never repay kindness; you can only pass it on.

When my blood counts bottomed out, sometimes I just couldn’t do anything, no matter how badly I wanted it. My mom and my husband’s aunt Carolyn took turns traveling to our house to help. Our neighbors, friends and co-workers helped so much, bringing food, taking the kids to school, going to the treatments with me, sending cards and much more. The incredible outpouring of kindness and support we got was overwhelming. Later at Camp Bluebird, I told my friend, John, who had multiple myeloma, how I wished so much to pay these people back for everything they did. “You can never pay them back, you can only pass it on,” he told me. That was a powerful, life-changing lesson.

Go ahead and make plans; just don’t fall in love with them.

Joy had lung cancer with brain metastasis. One night at support group she was telling us about upcoming trips she had planned and we were all talking and laughing with each other when a newly diagnosed newcomer to the group interrupted to say she did not understand how we could laugh and make plans when things seemed so grim and uncertain. Joy said something I will never forget. “It’s all right to make plans, just don’t fall in love with them.” Truly wise advice for anyone.

Suit up, show up and shut up.

In the spring of 2007, I signed up to walk a half marathon with Gilda’s Gang. The 14-week training schedule was the first challenge. We met every Saturday morning at 7 a.m. to do our long walks, starting at 3 miles and increasing to 10. It was January. I was full of complaints: It’s too early. It’s too cold. It’s raining. It’s snowing. It’s too hot. It’s too far. I’m tired. On and on. Over the next 14 weeks, a lesson in humility, gratefulness, grace and unrelenting spirit came to me in the person of Gail Addestone.

Two and a half years earlier, Gail had been diagnosed with a very aggressive form of breast cancer when she was pregnant with her only child. She had to deliver her baby early, have a mastectomy, and start chemotherapy. When I met her, she was facing treatment for a cancer recurrence in her bones, brain and liver. Despite the chemo, radiation and steroids, she never failed to show up for training with a smile on her face and enthusiasm in her voice. I was given the privilege to walk many miles with Gail. So I stopped complaining and my motto became “show up, shut up and keep putting one foot in front of the other.”



It has now been 16 years since I first heard the words
 “you have cancer.” Time is one blessing that I have received,
 but that too many of my friends didn’t get.



PHOTO BY DANA JOHNSON

for other ways. I started participating in the Susan G. Komen Race for the Cure. I organized teams, designed T-shirts and walked with my friends. I joined the Tennessee Breast Cancer Coalition and the National Breast Cancer Coalition. I had the opportunity to go to Advocacy Training Conferences in Washington, D.C., and participate in grassroots lobbying. It was very empowering to walk the halls of Congress and exercise my Constitutional right to petition the government about issues that were important to me such as funding for cancer research. My family and I got involved with the local American Cancer Society Relay for Life. I volunteered at Camp Bluebird as a counselor. I volunteered, and then worked a dream job for five years, at Gilda’s Club Nashville, a free support community for people with any kind of cancer and their friends and family. (What I would have given to have had their special programs for children for my own family!) Then came an opportunity to work at Vanderbilt’s Department of Cancer Biology in the laboratory of Al Reynolds. I get the chance to see first-hand the dedication and determination of these cancer researchers. Most recently, I have become a research advocate for the Vanderbilt SPORE (Specialized Program of Research Excellence) in breast cancer (see “Patients as Partners,” pages 22-23).

At first, I spent a lot of time doing all of these things because I thought I might not have much time left. But I’m still here, so I just keep showing up. Forrest Gump was right; you don’t know what you are gonna get. No matter what you get in life, the only time to live it is now. Today is the most important day of your life.

The most meaningful and important parts of my cancer journey are my traveling companions. I had unbelievable support and help from my husband, mother, children, family, friends, co-workers, doctors, nurses, researchers and even strangers. I have witnessed astonishing strength and wisdom from fellow cancer survivors. These teachers showed me that you can live – and live well – despite cancer. Some have also shown that it is possible to die with grace, dignity and even thankfulness. I am so grateful, so I try to keep showing up. ☺

Editor’s note: The type of treatment Pam had, high-dose chemotherapy plus a stem cell transplant, was used extensively in the past to treat advanced breast cancer. However, the majority of women who received this therapy in the 1990s did so outside the setting of a clinical trial. In the late 1990s, studies were launched to evaluate the treatment, and the results of three reported in 2000 were mixed – two found it was no more effective than standard treatment and the third was discredited due to fraud and misconduct by the lead investigator. Today, studies are ongoing, but this approach remains experimental.



web link

Learn more about Gilda’s Club and find a Clubhouse near you at www.gildasclub.org.

Pietenpol Named to Lead Vanderbilt-Ingram Cancer Center

Jennifer Pietenpol, Ph.D., was named in January to lead the Vanderbilt-Ingram Cancer Center and its nearly 300 researchers and physician-scientists as director.

Pietenpol became interim director last February, when Ray DuBois, M.D., Ph.D., stepped down to become provost/executive vice president at M.D. Anderson Cancer Center. She quickly emerged as a strong and respected leader with the right mix of skills for the role, said Harry Jacobson, M.D., vice chancellor for Health Affairs at Vanderbilt University Medical Center.

Pietenpol, who also became B.F. Byrd Professor of Oncology, said she was honored to be in a position to bring together the strengths of an outstanding group of people for what she calls one of the most important goals – making a difference in the lives of cancer patients.

“We have tremendous depth of talent and dedication among our faculty and staff,”

she said. “I’m willing to do whatever it takes to ensure that everyone on the team has what they need to continue their outstanding work.”

Pietenpol, also professor of Biochemistry, joins five other women at the helm of National Cancer Institute-designated Cancer Centers, which form a foundation of cancer research and advancing cancer treatment in the United States.

A member of the Vanderbilt faculty since 1994, Pietenpol has served as the center’s associate director for basic science and translational research programs since 2002, and was an Ingram Professor of Cancer Research. She is a past program leader for Signal Transduction and Cell Proliferation, one of seven research programs in the center.

Over the past year, Pietenpol has overseen progress in an expansion that will double the capacity of the cancer outpatient clinic and chemotherapy infusion center, and she has worked closely with other leaders in the ongoing development of a new strategic

vision for cancer care. The center recently edged into seventh place in National Cancer Institute funding and became a member of the prestigious National Comprehensive Cancer Network, an alliance of 21 of the world’s leading centers working together to improve cancer care.

After completing her doctoral degree in cell biology at Vanderbilt in 1990, Pietenpol served in the laboratory of Bert Vogelstein, M.D., at Johns Hopkins Oncology Center (now the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins).

Her own research focus is on tumor suppressor and cell cycle checkpoint signaling pathways in normal cells and how these pathways malfunction in tumor cells. The ultimate aim of her work is to define molecular changes that occur frequently in tumor cells and to use these alterations as targets for treatment. Currently, the Pietenpol laboratory is funded by the NCI, the Department of Defense and the Susan G. Komen Foundation.

– by Cynthia Manley

Julie Means-Powell



PHOTO BY NEIL BRAKE

Avoiding Chemo-Caused Heart Failure Aim of Collaboration

A tragic twist to cancer treatment is that sometimes the very therapy that saves a life can also create other serious, life-altering health problems. These can include effects on the heart.

Now, Vanderbilt-Ingram Cancer Center oncologists are teaming up with their colleagues in the Vanderbilt Heart and Vascular Institute to better understand why and how some cancer therapies cause heart failure and what can be done to prevent it.

“We hope that heart failure may, at

some point, be preventable when we can identify patients who are at increased risk of developing congestive heart failure and develop a treatment plan that gives them the best chance of breast cancer survival with the least risk of cardiotoxicity,” said oncologist Julie Means-Powell, M.D. “Wouldn’t that be nice if patients didn’t have to deal with breast cancer AND congestive heart failure?”

Although at least one of the chemotherapies that causes heart failure has been used for three decades, how it causes the problem is not well understood, said cardiologist Douglas Sawyer, M.D., Ph.D. He estimates that about one in every 100 cancer patients treated with these cancer therapies goes on to develop congestive heart failure, and two out of every 100 heart transplant patients have heart failure related to cancer therapy.

“The prediction is that number will grow as rates of cancer go up compared to heart disease,” he said. “In addition, there are new cancer therapies coming out that have effects on the heart, and those are not well understood.”

How the heart repairs itself has been the focus of Sawyer’s basic science research program for the last decade.

“From the time your heart is about 10 years old, the muscle cells in it have to last the rest of your life. The heart cells have to maintain and repair themselves,” he said. “Herceptin appears to interrupt those normal reparative mechanisms and allow for damage to take place. So in this case it’s not because the cancer therapy is causing damage, but because it interrupts the normal maintenance system.”

“It’s like if you stopped changing the oil in your car, as opposed to putting something bad in your car.”

Sawyer and his colleagues hope to begin clinical trials soon to look for early markers of cardiac dysfunction in breast cancer patients receiving anthracyclines, the mainstay of treatment for a broad range of malignancies including breast cancer, leukemia, lymphoma and sarcoma. They will also study patients receiving anthracyclines in combination with the targeted breast cancer drug Herceptin.

– by Kathy Whitney



PHOTO COURTESY LEADERSHIP MUSIC



Leadership Music Lauds Preston for Her Career, Commitment

Frances Preston, music industry icon and charter member of Vanderbilt-Ingram Cancer Center's Board of Overseers, was honored last fall with the Leadership Music Dale Franklin Award for 2007.

During a sold-out event at the Schermerhorn Symphony Center in Nashville, the former president and CEO of Broadcast Music Inc. was honored for her leadership and dedication to the music industry during her distinguished career.

Proceeds from the event will support the Frances Williams Preston Laboratories at the Vanderbilt-Ingram Cancer Center, directed by Vanderbilt-Ingram's director emeritus, Hal Moses, M.D. Moses thanked Leadership Music for honoring Preston and helping to direct funds from the evening to support cancer research.

"Frances' legacy in the music industry is clear to all those who have worked with her, but I also can attest to the impact of her leadership on the Vanderbilt-Ingram Cancer Center," he said. "Her gracious example of accepting

From left, Stan Mores, Hal Moses, M.D., and Orrin Ingram celebrate with Frances Preston at the Leadership Music Dale Franklin Award Dinner. Leadership Music directed proceeds from the event to support the laboratories at Vanderbilt-Ingram that bear Preston's name.

nothing less than excellence in all she does inspires us every day to do better and to reach farther in our fight against cancer."

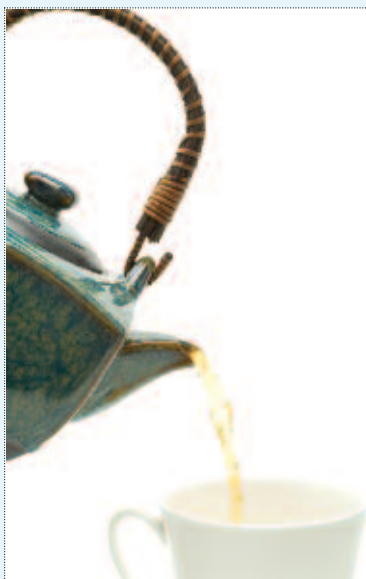
Singer and songwriter Vince Gill hosted the gala, which was attended by well-known entertainers as well as leaders in business, politics and medicine. Performers and those giving video tributes included Sheryl Crowe, Clive Davis, Dolly Parton, Big & Rich and Al Gore. Preston's favorite performance was given by her grandson, Taylor Preston, who serenaded her with "Forever Young."

A Nashville native, Preston has influenced and nurtured the careers of thousands of songwriters, performers and publishers during her five-decade career at BMI.

She was most recently a consultant to BMI, focusing on the company's international relationships and its public policy agenda.

Retired from BMI, Preston continues her role as a music industry consultant and advocate for cancer research. She is president of the T.J. Martell Foundation, which founded and funds the Preston Laboratories.

— by Dagny Stuart



DRINKING TEA IMPACTS CANCER RISK

For Asian women, rates of endometrial cancer increase when they move to the United States, suggesting that behaviors in their home country offer some protection against this disease. In particular, Asian diets include foods like tea and soy that are high in polyphenols — plant chemicals that inhibit the activity of aromatase, the enzyme encoded by the CYP19A1 gene.

Variants in the gene have been linked to endometrial cancer.

Xiao Ou Shu, M.D., Ph.D., and colleagues examined the interaction of these dietary factors with genetic variations, or polymorphisms, in CYP19A1. They report in the *American Journal of Epidemiology* that women who consumed less soy and tea had a lower risk of endometrial cancer.

However, only tea consumption modified endometrial cancer risk linked to three CYP19A1 polymorphisms. The findings suggest that tea polyphenols may modify the effect of polymorphisms in the CYP19A1 gene on the development of endometrial cancer and highlight the importance of gene-environment interactions on disease risk.

— by Leigh MacMillan

HPV Linked To Head and Neck Cancers

You've probably seen the ads for the new vaccine that protects young women against infection with human papillomavirus (HPV) and the promise the vaccine holds for preventing most types of cervical cancer.

There's another devastating form of cancer linked to HPV infection — head and neck cancer — and almost no one is talking about it.

"I think the public and most physicians have no idea that HPV relates to head and neck cancer," said Wendell Yarbrough, M.D., Vanderbilt-Ingram Cancer Center surgical oncologist. "In cancers of the oropharynx, which includes the tonsils, the base of the tongue, and part of the throat, about half of those tumors are HPV-positive. In the oral cavity, between 10 and 15 percent of tumors test positive for HPV, although here at Vanderbilt-Ingram we're seeing up to 20 percent."

HPV is one of the most common sexually transmitted diseases in the world. The Centers for Disease Control and Prevention (CDC) estimates nearly 6.2 million new genital HPV cases occur in the United States each year. Now researchers have documented a rise in some types of head and neck cancer

related to HPV. The spike coincides with reported changes in sexual habits among young people, including earlier age of sexual activity and an increase in oral sex.

The good news is that patients whose tumors are HPV-positive may do better than those whose cancers are HPV-negative. In fact, in a study of patients with cancer of the oropharynx, those whose tumors were HPV-positive had higher rates of response to treatment and lower risks of cancer progression and death than those whose cancers were HPV-negative, reported Anthony Cmelak, M.D., a Vanderbilt radiation oncologist, along with colleagues from Johns Hopkins Medicine, Dana Farber Cancer Institute, Stanford University and Fox Chase Cancer Center.

There are more than 100 subtypes of HPV. Types 16 and 18 usually are implicated in cervical cancer and are found in HPV-positive head and neck cancers. The HPV vaccine is effective against those subtypes but the vaccine is only approved for use in girls and women ages 9 to 26.

The discovery of a link between the virus and head and neck cancer raises the possibility of vaccinating young men, Yarbrough said.

— by Dagny Stuart

Head and neck cancer surgeon Wendell Yarbrough, M.D., screens a patient at Vanderbilt's annual Yul Brynner Head and Neck Cancer Awareness Day event.



PHOTO BY DANA JOHNSON

Sam Chang, M.D.

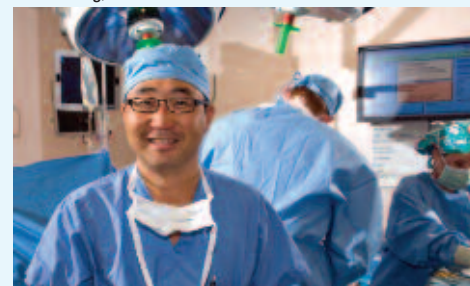


PHOTO BY NEIL BRAKE

Vanderbilt First in Tennessee to Test Prostate Cancer Therapy

Urologic surgeons at Vanderbilt are the first in Tennessee to test a new, minimally invasive surgical procedure to treat prostate cancer. The Albatherm procedure uses high intensity focused ultrasound (HIFU) to destroy malignant prostate tissue without any incision.

The technique has been used in Europe for more than a decade to treat localized prostate cancer in select groups of patients. It works by delivering precisely focused beams of high intensity ultrasound through a series of targeted shots. At the point where ultrasound is focused, the sudden and intense absorption of the beam creates a rapid temperature increase in the tissue, which destroys cells in the targeted zone.

Fifteen patients will be enrolled in the study at Vanderbilt. Eventually, 18 sites will participate, with 12 of them offering HIFU and the other six offering cryotherapy for the study's control group. Other clinical trial participants include Duke University, Georgetown Medical Center, Baylor College of Medicine and the Cleveland Clinic.

"This is the first FDA-approved study with this device for the treatment of primary, localized prostate cancer," said Sam Chang, M.D., who is a co-investigator along with colleagues Michael Cookson, M.D., and Peter Clark, M.D. "In Europe, HIFU is the fastest growing treatment for localized prostate cancer. Right now, through this study, this is the only way in the U.S. for patients to receive this type of therapy in a controlled and safely regulated manner."

For information about the trial, call the Department of Urologic Surgery at (615) 343-2120.

— by John Howser



Get more news about Vanderbilt-Ingram by visiting www.vicc.org/news and subscribing to our RSS feed.



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:

Tumor "tag" shines light on cancer response

A technique that specifically "tags" tumors responding to chemotherapy may offer a new strategy for determining a cancer treatment's effectiveness within days of starting treatment. A team at Vanderbilt-Ingram reports in *Nature Medicine* the identification of a small protein that specifically recognizes tumors responding to chemotherapy. They show that the protein, when tagged with a light-emitting molecule, can be used to visualize cancer response in mice just two days after starting therapy. Currently, response to chemotherapy is determined by measuring changes in tumor size with imaging techniques like CT and MRI (magnetic resonance imaging). "It takes two to three months of cancer therapy before we can determine whether the therapy has been effective for a patient," says senior investigator Dennis Hallahan, M.D. "If we can get that answer within one to two days, we can switch that patient to an alternative regimen very quickly."

Cancer-related protein yields to 'peer pressure'

When it comes to cancer, the protein EphA2 appears heavily influenced by peer pressure. This protein is commonly expressed in aggressive breast cancers. In some circumstances, it seems to promote cancer growth and metastasis, but at other times, it appears to inhibit tumor growth. Which role it plays depends in particular on the presence of another famous human breast cancer gene, Her2, write Jin Chen, M.D., Ph.D., and colleagues

in *The Journal of Clinical Investigation*. In cell and animal models, the researchers found that EphA2 interacts with Neu, the rodent version of the human Her2 gene, and this complex activates cell signaling pathways that promote cell growth and motility. The results suggest that EphA2 cooperates with Neu (Her2) to promote tumor progression and could be a potentially useful target for Her2-dependent tumors, particularly in combination with a drug like Herceptin, which targets Her2. Chen is studying whether cells resistant to Herceptin might benefit from treatment with EphA2-targeted treatments, which are currently in development.

Finding could help time cancer treatment

Researchers led by Li Yang, Ph.D., and Hal Moses, M.D., have found a clue to the seemingly contradictory nature of the protein TGF-beta that could someday help doctors determine the best timing for cancer treatment. They report in *Cancer Cell* a critical role for the body's own immune cells in causing TGF-beta's change from a tumor suppressor in early stages of cancer to a promoter of tumor growth and spread in advanced cancer. This dual identity of TGF-beta presents a serious patient care challenge. Treatments designed to inhibit TGF-beta signaling are currently being developed and tested – but what if treatment is given when the protein is acting as a tumor suppressor and inadvertently promotes cancer progression instead? In animal models of breast cancer,

the investigators found immune cells called myeloid immune suppressor cells (MISCs) in greater numbers in tumors in which TGF-beta function had been eliminated. The cells were found mostly at the "invasive front" of tumors, suggesting that they are called to where the tumors are spreading into normal tissue. These cells produce TGF-beta and a kind of enzyme called MMPs that are known to be important in cancer metastasis. The investigators suggest that recruitment of these cells is important in the switch from tumor suppressor to promoter. MISCs are known to circulate in the bloodstream, so it may be possible to develop a blood test for these cells that could indicate whether timing is right for TGF-beta inhibitor treatments.

Molecule may put brakes on head and neck cancers

A molecule that is lost in about one-third of a type of head and neck cancers has properties that suggest it acts to put the brakes on cancer, a team led by Wendell Yarbrough, M.D., reports. "If loss of LZAP is a mechanism that enables head and neck cancer formation or tumor growth, understanding how it works will, in the long run, help us to better treat these tumors," says Yarbrough. The investigators were looking for proteins that regulate the tumor suppressor ARF. The team screened for proteins that bind to ARF and found LZAP. The new protein had the interesting ability to inhibit cell growth. A new tumor suppressor gene doesn't come along every day, making the findings very exciting, he says. The investigators linked LZAP activity to NF-kappa-B, a family of transcription factors that regulates genes involved in inflammatory and immune responses and that has been implicated in tumor

development. The current paper reports that LZAP inhibits NF-kappa-B, and that when LZAP is lost, NF-kappa-B activity increases. The work appeared in *Cancer Cell*.

This work supported in part by the National Institutes of Health, the Ingram Charitable Fund, the T.J. Martell Foundation, the Robert J. and Helen C. Kleberg Foundation, the Barry Baker Laboratory for Head and Neck Cancer Research and others.

Newly identified section of receptor may be target

Many targeted anti-cancer agents try to disable or prevent activation of the receptor for the epidermal growth factor, which drives cell growth characteristic to cancers. A study by Graham Carpenter, Ph.D., and colleagues identifies a portion of the EGR receptor – previously an unrecognized contributor to the activation process – as essential for the receptor to be active. In addition to increased understanding of this important therapeutic target, the paper suggests a new site for attacking this regulator of cancer growth. The work appeared in the *Proceedings of the National Academy of Sciences*.

Work reported in Journal Watch was supported in part by the National Institutes of Health, the Ingram Charitable Fund, the T.J. Martell Foundation, the Robert J. and Helen C. Kleberg Foundation, the Barry Baker Laboratory for Head and Neck Oncology, and others.



web link

More info about our research at
www.vicc.org/research



NoogieFest!

Vanderbilt-Ingram Cancer Center and Gilda's Club Nashville joined together last fall to celebrate Childhood Cancer Survivors Day. The event was filled with fun for the children (aided by volunteers from Vanderbilt School of Medicine) and information and networking for parents.

Top left, Kathryn Mast dives into her own cookie creation. Top right, Jillian Pasley shows off her artwork. Bottom left, Matthew Mast tries his hand at juggling. Bottom right, Preston Allen peers through his lion mask.

PHOTOS BY NEIL BRAKE

Found in Translation

A Middle Tennessee woman illustrates
the ultimate “return on investment”
for decades of research.

page

20



PHOTO BY TAMARA REYNOLDS

momentum

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691 Preston Research Building
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