

*Moving toward a future without cancer.*

# momentum

IN THIS ISSUE: GIFT OF FRIENDSHIP • STRANGE CASE OF TGF- $\beta$  • RECIPE FOR HEALTH



## Predicting colon cancer

Can genetics help tackle  
the second leading cancer killer?

## On the cover:

While much is known about the genetic alterations involved in colon cancer, much remains hidden – especially about how to best use this knowledge to prevent, diagnose or treat the second leading cancer killer. See page 8.

## Pictured below:

Cultured colon cancer cells showing the nuclei stained blue, the actin cytoskeleton in red and plectin – a protein that interacts with cytoskeletal actin, affecting its behavior – in green. This subtype of plectin promotes the migration of cells and may affect metastasis. Image by Lorna McInroy/Wellcome Images.

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*Moving toward a future without cancer.*

# momentum

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[www.vicc.org/momentum](http://www.vicc.org/momentum)





JOE HOWELL

## Director's letter

For more than 50 years, the Magic 8-Ball® has been a perennial favorite, today inspiring numerous knock-offs and Internet versions. While we know it can't really predict the future, it's difficult to resist. Ask a question – “Will my grant get funded?” – turn it over, and the answer appears in the window.

It's all in fun, so answers like “cannot predict now” or “reply hazy, try again” are easy to brush off. Just keep trying until the answer we want reveals itself.

But when you are facing cancer, your questions demand less ambiguous replies. At the Vanderbilt-Ingram Cancer Center, we work hard to answer those questions in an evidence-based manner. As we develop a deeper understanding about the molecular defects in a cancer cell, we're using new information to improve treatment and early diagnosis, tailor therapy and prevent disease.

As this issue of *Momentum* went to press, National Colorectal Cancer Month was just getting under way. Activities and education abound this spring, aimed at increasing awareness of the second leading cancer killer. It is a cancer that typically progresses in a predictable way, offering opportunities to intervene, but not everything is known about the molecular defects that play a role in this disease. In “Predicting Colon Cancer,” you'll read about work here and elsewhere aimed at unlocking the secrets behind this disease and using that knowledge to improve diagnosis, treatment and prevention.

As we develop a deeper understanding about the molecular defects in a cancer cell, we're using new information to improve treatment and early diagnosis, tailor therapy and prevent disease.

Also in this issue, you'll learn about a protein called transforming growth factor beta, sometimes referred to as Jekyll and Hyde, and you'll meet the pioneering scientist, Dr. Hal Moses, who helped solve the mystery of its dual nature. Other stories explore the important role of the oncology nurse in the lives of patients and families; take you behind the scenes to meet the medical physicists who have great expertise in the design of complex radiation therapy plans; and highlight the creativity and commitment of dozens of volunteers across the state who are part of the Tennessee Comprehensive Cancer Control Coalition.

Last but not least, throughout the issue, you'll meet individuals like David Lipscomb and Stephanie Crowe whose worlds were rocked by a cancer diagnosis. In “A Marriage of Music and Medicine,” you'll read about a longstanding partnership to make life better for folks like them and future generations. For 15 years, the T.J. Martell Foundation has fueled promising discoveries in our Frances Williams Preston Laboratories – it is a relationship that has yielded not only promising discoveries but also great friendships.

As always, we hope you enjoy this issue, and that you'll share your copy with others. We are proud to report on our work, which ultimately is focused on answering one question – can we achieve a world without cancer?

As the Magic 8-Ball® might say, “It is decidedly so.”

## ACLOSERLOOK

CHARLES COFFEY, PH.D.

Director of Medical Physics, Vanderbilt-Ingram Cancer Center



**Q: A 0.2 kilogram softball is thrown with a momentum of 3.1 kilogram-meters per second. What is the velocity of the softball?**

It was in high school physics, solving these kinds of problems, that Charles Coffey, Ph.D., first found his calling. He remembers being thrilled to learn how the laws of physics explain the behavior of the world around us.

"I started problem solving in that class," he says. "And I'm just as excited today about solving problems as I was then."

The problems have gotten a bit trickier. Today, Coffey is the director of Medical Physics at the Vanderbilt Center for Radiation Oncology.

Medical physicists play a key, behind-the-scenes role in any diagnostic procedure or treatment that involves radiation, whether it's conventional X-ray, CT imaging, or radiation therapy for cancer. Diagnostic physicists work with radiologists to capture the best images; therapy physicists, like Coffey, are the "pharmacists" of the radiation oncology team.

"The physician decides on a course of treatment and relies on medical physicists to help deliver that radiation prescription," Coffey explains. "The physicist's role is to determine – using everything from simple logic to very complicated calculations – how best to treat the tumor and spare the normal tissue."

Coffey points to a computer screen showing a CT image of a tumor and nearby tissues. The tumor has a series of colorful lines around it that look like elevation lines on a topographic map and indicate the radiation dose. Getting these lines to match the tumor, "by varying the size and energy of the field, the radiation angles, and a lot of other things," is part of treatment planning, Coffey explains.

Therapy physicists spend about 60 percent of their time involved in treatment planning. They spend the rest of their time assuring that every step of the process – "from A to Z," Coffey says – is accurate.

They ask questions: Is the imaging study correct? Is the treatment planning algorithm correct? Are the machines (that deliver the radiation) calibrated? Is the delivery of the dose correct?

"Everywhere along the road there are quality assurance issues that we check routinely – some daily, some monthly, some annually," he says.

While Coffey loves solving complex problems, he is perhaps even more excited about his role in training the next generations of medical physicists.

When Coffey came to Vanderbilt in 1993, the health and medical physics program that had been in place in earlier decades was inactive. With support from other faculty members, he helped revive the two-year master's degree program, which now boasts 21 students. Plans to add a professional doctorate program await university approval. Vanderbilt would be the first institution to offer such a degree, which may be the way the field moves for training board-certified therapy physicists, Coffey says.

Another of Coffey's joys – softball – has found its way into the medical physics program. Two teams with physics-inspired names – Accelerators and Electrons – are among the more competitive in Vanderbilt's intramural system, and Coffey's office has the framed championship shirts to prove it.

"The second question we ask students interviewing for the master's program is whether they can play softball," he says, laughing. He's quick to add that softball skills are not a requirement for admission – just a penchant for solving problems (and the math and science background to go with it).

Having a homerun swing and a strong arm wouldn't hurt though.

**A: 15.5 meters per second – about 35 miles per hour – pretty fast for slow-pitch softball.** 🏈

– by Leigh MacMillan



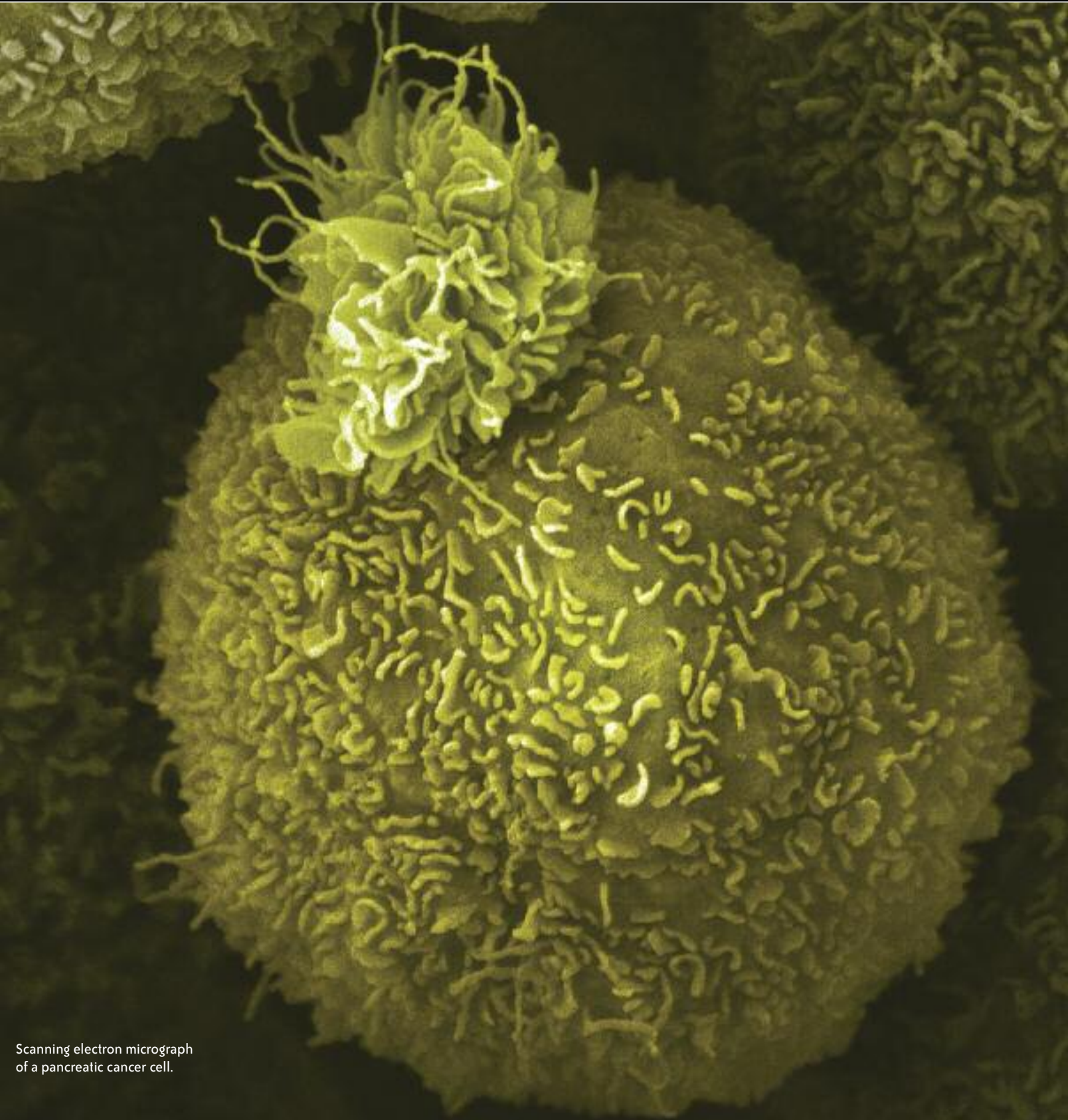
web link

More information about the Vanderbilt medical physics master's program at: [www.vanderbilt.edu/msmp](http://www.vanderbilt.edu/msmp)





# SPOTLIGHT: PANCREATIC CANCER



Scanning electron micrograph  
of a pancreatic cancer cell.



# Going the *distance*

Marathoner-in-training takes on pancreatic cancer

By Dagny Stuart | Image by Anne Weston, Wellcome Images

The day David Lipscomb was diagnosed with pancreatic cancer he had run two-and-a-half miles as part of his training for Nashville's Country Music Marathon. At age 44, with a wife, Robi, and two college-age sons, Lipscomb was active and seemingly healthy. He and a partner were running Overflow Management, a Christian music artist management company based in Franklin, Tenn. He had no idea that his recent bouts of intense nausea were symptoms of a silent killer that would threaten this fast-paced life.

"On Christmas Eve we ate a big meal with our family, and that night I was violently ill," Lipscomb remembered. The same thing happened after a big meal a week later on New Year's Eve. His family physician thought the symptoms could be the flu. But a few days later when Lipscomb returned from that run, Robi looked at his eyes and realized they were yellow.

"I told him this is something serious," Robi said. "I had seen some TV shows, and I knew that was a bad thing."

Hours later in a local hospital emergency room – after an ultrasound, MRI and a CT scan – the ER doctor gave the couple the grim diagnosis. The tests had revealed a tumor in Lipscomb's pancreas; it was almost certainly cancerous.

"When I was in the MRI, I was praying to be peaceful. I had this sense that God was preparing me for something bad," Lipscomb said. He had no idea how difficult the coming journey would be.

Cancer of the pancreas is an especially lethal disease. According to the National Cancer Institute there were approximately 37,680 new cases in 2008 with 34,290 deaths, making cancer of the pancreas the fourth leading cause of cancer death in this country. Only 5 percent of patients are still alive after five years.

The pancreas is a thin, elongated gland about six inches long that lies behind the stomach. It produces juices to help digest food and hormones to help control blood sugar levels. In the early stages of pancreatic cancer, there may be no symptoms at all. Even when the disease advances, symptoms like abdominal discomfort, back pain or weight loss may be mistaken for other diseases. Many patients don't suspect they are sick until they develop yellow skin or eyes, a symptom of jaundice. Because of these often subtle symptoms, most pancreatic cancer is diagnosed at an advanced stage when it is much more difficult to treat.

Until his bouts with severe nausea and jaundice, Lipscomb was unaware that he was sick, suffering from a form of cancer that had not yet gained wide recognition in the public consciousness.



The Lipscomb family at the wedding of son David Jr. (center). Left to right: Robi, daughter-in-law Amanda, David Jr. (DJ), David, and son Dale.

**"I want the public to understand this is a very serious and terrifying disease, and it's under the radar."**

Only recently has the spotlight begun to focus on pancreatic cancer – due in part to actor Patrick Swayze's diagnosis and Carnegie Mellon University Professor Randy Pausch's "The Last Lecture," a primer for his children on living your dreams, that became an Internet phenomenon and sparked TV appearances and a book. Pausch died of the disease last year at age 47.

"There aren't many celebrities talking about it or holding fundraising events on TV because they're not around to do that," Lipscomb said. "I want the public to understand this is a very serious and terrifying disease, and it's under the radar."

After a biopsy, Lipscomb discovered he was one of the luckier patients; his tumor was blocking a bile duct at the head of the pancreas – the one place where tumors may be surgically removed.

After doing some research through the Pancreatic Cancer Action Network (PanCAN) and other organizations, Lipscomb decided to be treated at a comprehensive cancer center by a surgeon who performed a high volume of aggressive pancreatic cancer operations. He found Nipun Merchant, M.D., associate professor of Surgery at Vanderbilt-Ingram Cancer Center, who performs nearly sixty complex pancreatic cancer operations a year.

"Surgery is the primary treatment," said Merchant.

"Unfortunately only about 15 to 20 percent of patients are appropriate for surgery. If the tumor has already spread beyond the confines of the pancreas – to the liver or the lining of the abdomen – taking out the tumor in the pancreas is not going to help the patient since all of the tumor will not be removed."

The location of the tumor is also vitally important. The head of the pancreas wraps around two major blood vessels that supply blood to the liver and the intestines.

"If the tumor is wrapped around those, and if we cannot remove all of the tumor – even if we leave a little bit behind – it's the same as not doing the operation," Merchant explained.

"In the past, these operations were considered high-risk," Merchant said. But thanks to improvements in surgical techniques, "in high-volume cancer centers, the mortality for this procedure is less than 2 percent. We're very aggressive here at Vanderbilt-Ingram when it comes to operating in tight spots."

Dramatic improvements in imaging also help physicians identify the best candidates for surgery. "We are so much better now at taking the appropriate patients to surgery," Merchant said. "There is a lot of progress being made in terms of defining characteristics of which tumors are resectable, unresectable or borderline resectable based on the involvement of the surrounding blood vessels."

The Lipscomb family knew how fortunate they were that David was a candidate for surgery, which provides the only hope for a cure.

"It was a three-centimeter tumor and honestly, had it been a centimeter either way and not on that bile duct, we wouldn't be having this conversation," Robi explained.

Still, David knew the surgery would be tough.

On Jan. 22, 2008, Merchant performed the Whipple procedure, removing one-third of Lipscomb's pancreas, his gallbladder, a small piece of his liver, and part of his small intestines.

While the surgery went well, there were setbacks and Lipscomb spent nearly three weeks in the hospital. Over the next few months he underwent chemotherapy and then combination chemo-radiation therapy.

Lipscomb's medical oncologist, Laura Williams Goff, M.D., prescribed a chemotherapy drug called gemcitabine.

"I always feel good about offering gemcitabine to patients with pancreas cancer because it was approved on the basis of improvement in clinical benefit, improvement in pain and overall energy levels," said Goff, an assistant professor of Medicine at Vanderbilt-Ingram. "Most people don't lose their hair, and they have minimal nausea and vomiting. It's a pretty well-tolerated regimen."

While chemotherapy after surgery does improve survival, it is difficult to cure the disease. Some patients also receive radiation therapy, which may be helpful especially for high-risk tumors.

"There has been a lack of progress in clinical trials for adjuvant therapy after surgery," said Merchant. "Based on all of the





clinical trials so far, there is still a great deal of controversy regarding the role of radiation therapy. It's unfortunate that we haven't been able to come to a consensus because there are such limited options for our patients."

Since 80 percent of patients are not eligible for surgery, cancer researchers are diligently trying to develop new drug treatments for pancreatic cancer. So far, the only targeted therapy approved by the Food and Drug Administration (FDA) is erlotinib, known commercially as Tarceva. While the drug normally extends life by a few weeks, the fact that it works at all is reason for hope in a disease that has proved difficult to understand and treat. Even when patients are successfully treated with surgery, chemotherapy, radiation or Tarceva, the chance of a recurrence is dramatic; the cancer returns in about 80 percent of patients.

Researchers are also starting to identify the genetic pathways that mark the progression of the disease.

"We have known for some time that the K-ras gene is mutated and overactive in pancreas cancer," Goff explained. "It seems to

happen early in the development of pancreas cancer, but figuring out how to turn it off or to target that abnormal K-ras has so far eluded us."

Hal Moses, M.D., Director Emeritus of Vanderbilt-Ingram, and colleagues have developed a mouse model of pancreatic cancer – by coupling a K-ras mutation with another mutation – that closely resembles human disease. This model could provide new opportunities for studying the disease's progression and for investigating potential therapies.

Goff hopes that it will be possible to individualize chemotherapy or targeted therapies for different types of pancreas cancer.

"There have been preliminary efforts to try to segment types of pancreas cancer by groups of genes – similar to what has been done for breast cancer or lung cancer – but that research is very early and is not ready for prime time," she said.

The successes in treating and curing breast and colon cancer make the lack of success in pancreatic cancer even more frustrating for physicians and patients. And they all point to the same fact: the dramatic difference in levels of research funding. While pancreatic cancer is among the top five cancer killers, the disease constitutes less than 2 percent of the National Cancer Institute's research budget – far less than funding for other major cancer types.

"For more than 30 years we have been talking about waging a war on cancer," said Jordan Berlin, M.D., associate professor of Medicine and clinical director of Gastrointestinal Oncology at Vanderbilt-Ingram. "But when you look at the amount of money devoted to pancreatic cancer research, it's more like a skirmish."

"One of the reasons we have made so many inroads in treating breast or colon cancer is because we have devoted so many financial resources to basic and clinical research," Berlin said. "With an aging population, we are going to see many more pancreatic cancer patients, and we need to start focusing our research dollars on this disease."

David Lipscomb and family agree with that sentiment – and hope to help raise public awareness of this disease.

Nine months after surgery, Lipscomb had regained some of the weight he lost and was starting to exercise again. He had even managed to keep working during much of his recovery. But the battle is far from over.

"Even though the percentages are bleak, somebody always beats the percentages," Lipscomb said. "Why not me? Somebody has to. How humbling to think only two out of 10 patients who get this can have surgery. I can't help but feel hopeful because I've already beaten the odds." 🍀

*Editor's note: As Momentum was going to press, David's cancer returned and progressed quickly. He passed away on Feb. 25. For those who would like to help patients like David, his family requests that donations be made to the Pancreatic Cancer Action Network ([www.pancan.org](http://www.pancan.org)), an organization that sponsors research and advocates for more public awareness of this disease.*

## PANCREATIC CANCER RISK FACTORS

While nobody knows the exact cause of pancreatic cancer, the following risk factors are known to increase a person's chance of developing the disease.

### Age

The likelihood of developing pancreatic cancer increases with age. Most pancreatic cancers occur in people over the age of 60.

### Smoking

Cigarette smokers are two or three times more likely than nonsmokers to develop pancreatic cancer.

### Diabetes

Pancreatic cancer occurs more often in people who have diabetes than in people who do not.

### Being male

More men than women are diagnosed with pancreatic cancer.

### Being African-American

African-Americans are more likely than Asians, Hispanics or whites to get pancreatic cancer.

### Family history

The risk for developing pancreatic cancer triples if a person's mother, father, sister or brother had the disease. Also, a family history of colon or ovarian cancer increases the risk of pancreatic cancer.

### Chronic pancreatitis

Chronic pancreatitis is a painful condition of the pancreas. Some evidence suggests that chronic pancreatitis may increase the risk of pancreatic cancer.

Source: National Cancer Institute



OUTLOOK  
GOOD



# Predicting colon cancer

**Can genetics help tackle the second leading cancer killer?**

Nobody “expects” a 21-year-old to have advanced colon cancer. But sometimes they do, says Dan Beauchamp, M.D., a surgical oncologist at Vanderbilt-Ingram Cancer Center. He recalls just such a case: a 21-year-old with rectal bleeding that had persisted for three years before coming to Vanderbilt University Hospital and the Vanderbilt-Ingram Cancer Center with symptoms of bowel obstruction. The patient hadn’t had a colonoscopy – colorectal cancer just wasn’t at the top of the list of concerns for such a young patient or his health care providers.

When the patient finally had a colonoscopy, the test revealed a large rectal tumor. Further workup showed that the disease had already spread widely throughout his body, and because of his severely weakened and malnourished state, little could be done to intervene.

*By Melissa Marino | Photograph by Joe Howell*





colon cancer diagnosis often comes as a complete shock. While the 21-year-old patient had an obvious warning sign – although it was ignored until too late – many others have no such signal.

Colonoscopies are still the best way to detect colorectal cancer while it is still curable. But even rigorous adherence to screening guidelines will fail to catch some cases of colorectal cancer.

Researchers hope that the proliferation of knowledge about the various genetic alterations that underlie colon cancer could offer some additional help in early diagnosis, targeted treatment and perhaps even prevention of colorectal cancer.

Fortunately, the genetic events that lead to the development of colon cancer usually take years to unfold, giving ample opportunity for intervening before the cancer advances.

Unfortunately, all the genetic alterations that contribute to colon cancer – and how best to exploit them for diagnosis and treatment – are unknown.

In a 2004 *Nature Medicine* review paper, cancer genetics pioneer Bert Vogelstein, M.D., at the Johns Hopkins University School of Medicine, noted “Cancer is, in essence, a genetic disease...(but) no single gene defect ‘causes’ cancer.”

“Most people think it takes about seven to 10 years to go from a normal colon to a cancer, maybe longer,” says Robert Coffey, Jr., M.D., Ingram Professor of Cancer Research and professor of Cell and Developmental Biology at Vanderbilt-Ingram.

Recently, Vogelstein and colleagues estimated that it takes approximately 17 years for a large benign tumor to evolve into an advanced cancer, but only two additional years for that cancer to acquire the ability to metastasize, or spread throughout the body.

All told, the entire process – from the first genetic misstep that initiates abnormal cell growth to metastatic cancer – can take 30 to 40 years, according to Vogelstein’s estimates.

“This provides a huge window of opportunity to detect tumors at a stage when they are still curable by conventional surgical methods,” wrote Vogelstein and colleague Kenneth Kinzler, Ph.D., in the *Nature Medicine* article. Perhaps more promising, the extended lead-time presents opportunities for prevention.

“Though less dramatic than cures,” they wrote, “prevention and early detection are perhaps the most promising and feasible means to reduce cancer deaths.”

#### Cannot predict now

Colon cancer starts in a single cell in the colon’s lining, or epithelium. This lone cell acquires a mutation – an error in the genetic code – that gives it a growth advantage. The most common mutations are in two categories of genes: tumor suppressors (which limit cell growth) and oncogenes (which promote cell growth). Researchers think that it takes at least five to seven mutations for a colon cancer to develop.

The earliest visible sign of trouble may be the development of microscopic lesions, called aberrant crypt foci, in the colon lining. The normal colon epithelium is not a flat, smooth surface but an undulating array of peaks and valleys (termed crypts). Under the microscope, aberrant crypts appear larger than normal colon crypts with a thickening of the epithelium. Later, these lesions may develop into small – but still benign – polyps (adenomas) that can progress to a full-fledged colon cancer (carcinoma).

From decades of research, various genetic mutations have been identified that correspond with each of these steps.

In 1988, Vogelstein and Eric Fearon, M.D., Ph.D., laid out the first genetic model for colorectal cancer development – colloquially called a “Vogelgram” – that illustrates the mutations correlated with the various stages of the disease.

The model has provided an important but simplified framework for understanding colon cancer progression. Vanderbilt-Ingram investigators – and cancer researchers around the world – are building on this classic model, looking for additional genetic events that contribute to colon cancer development in hopes of identifying points at which clinicians can intervene to prevent, slow or stop the cancer’s spread.

While the sequence of mutations represented by the model appear linear, it is clear that the path to colon cancer is a bit more nuanced.

“Colon cancer represents an accumulation of genetic events,” says Coffey. “But they don’t necessarily have to occur in some lock-step order.”

The first and most well-established step – the genetic alteration that seems to initiate most colon cancers – is a loss of

function of the APC (adenomatous polyposis coli) gene, a tumor suppressor gene.

“Most colon cancers are initiated, we think, in the same way,” says Beauchamp, the John Clinton Foshee Distinguished Professor of Surgery and the Chair of the Section of Surgical Sciences.

APC mutations are found in about 80 percent to 90 percent of colon cancers – both the rare inherited types and the more common sporadic types. When a cell loses function of APC, the cell’s natural ability to restrain cell growth and division is lost. This loosening of cell growth restrictions sets the stage for a cancer to form.

Because nearly every cell in our bodies has two copies of the gene – one from each parent – losing one copy of APC doesn’t automatically initiate cancer.

“If you have one mutation in APC, it’s not enough to immediately get a cancer or even a polyp,” Beauchamp explains. “The other copy of the gene has to be lost or silenced somehow.”

In a condition known as familial adenomatous polyposis (FAP), colon cancer already has a head start. People with FAP inherit one “bad” or dysfunctional copy of the APC gene from a parent. But this only predisposes them to colon polyps and colon cancer. It takes an additional insult to the other “good” copy of the gene to initiate the development of polyps (or adenomas). These are benign growths, but if not removed, they almost always develop into cancer.

“Knowing the initiating event does not help us predict who is going to get cancer, except when there is a hereditary syndrome

(like FAP),” Beauchamp says. But the lessons learned from research on this pathway are providing potential targets for therapies that intervene to forestall the growth of a cancer.

APC is just a part of a much larger system, called the Wnt signaling pathway. The pathway is activated during the development of the early embryo, and it is highly regulated in adult cells. However in many cancers – colon cancer especially – this embryonic pathway becomes dysregulated, most often by mutations in APC.

“When you lose functional APC, one of the consequences is that you activate the Wnt pathway,” explains Coffey. When the pathway is activated, another molecular component of the pathway, called beta-catenin, is freed from the cell surface to go into the cell’s nucleus. There, he says, “it will turn on genes that we think are critically important in the development of colon cancer.”

So, even if a person has two normal copies of APC, mutations in other steps of this pathway – in beta-catenin, for example – can also activate the pathway, producing the same cancer-promoting effect. Vanderbilt developmental biologist Ethan Lee, M.D., Ph.D., has found that another pathway component, called Axin, is a central regulator of Wnt pathway activity.

Based on a mathematical model, “we can propose that controlling Axin levels and its turnover is the major way by which this pathway can be regulated,” says Lee, an assistant professor of Cell and Developmental Biology.

Using a test tube-based assay Lee developed to study Wnt signaling, his team has identified several compounds that inhibit the pathway.

“The idea is that if any of these compounds work out, they can be potential tools to study the pathway and – further down the line – as potential drugs.”

One of these, called VU-WS30, is showing promise: it inhibits the growth and viability of cultured cancer cells. Lee found that it works by inhibiting Axin degradation and stimulating beta-catenin degradation – pathway alterations that inhibit cell growth.

It’s an exciting lead, says Coffey. “If you lose APC...but you make enough Axin...you can compensate for the loss of APC.” And because the drug is already an FDA-approved compound (for diseases other than cancer), that would accelerate the process of testing it as an anti-cancer agent in humans.

### Signs point to... progression

While APC mutations and other mutations that activate Wnt signaling are necessary for the development of early polyps, the progression onward to colon cancer requires additional genetic alterations.

“Even though most cancers are initiated that way (by activations of the Wnt pathway), that doesn’t fully explain the behaviors of all cancers,” says Beauchamp. “It gets the ball rolling, but you can still have a wide diversity of tumor behavior downstream of that initiating event.”

Mutations in a gene called K-ras are associated with the progression from small polyp to large polyp. K-ras is an oncogene – a gene whose protein product promotes cell growth and division – and



CNR1 / PHOTO RESEARCHERS, INC.

A colon polyp (red) protrudes from the lining of the colon (shown in this colored barium X-ray). While usually harmless, colon polyps can become malignant, and are often surgically removed.



Dan Beauchamp (left) and Robert Coffey (right) are investigating the genetic factors that underlie colon cancer. Coffey directs Vanderbilt-Ingram's Specialized Program of Research Excellence in gastrointestinal cancer.

about 40 percent of all colon cancers have mutations that activate or “turn on” K-ras function when it shouldn’t be on, Beauchamp notes.

Like APC, K-ras is just one link in another chain of cell signaling molecules, called the MAP kinase pathway. This pathway also includes a protein called B-raf, and mutations in the gene encoding B-raf have also been identified in colorectal cancer.

A certain proportion of cancers – about half – will have a defect in a growth factor pathway called the TGF- $\beta$  (transforming growth factor beta) signaling pathway. In one type of hereditary colon cancer (called HNPCC, or hereditary nonpolyposis colorectal cancer), about 90 percent of patients have a loss of one piece of this pathway – the TGF- $\beta$  type II receptor.

Still other tumors may have mutations in other components of the TGF- $\beta$  pathway, called Smad proteins. Beauchamp is examining the roles of TGF- $\beta$  and the Smad proteins in the process of epithelial-mesenchymal transition – a reversion of cell behavior to a more embryonic state. This process is thought to be a critical – and potentially reversible – step in cancer progression.

Another growth factor, called EGF or epidermal growth factor, also seems to have an important role in this “establishment” phase of colon cancer.

Coffey and colleagues have shown that, in mice that carry the initiating mutation in APC, reducing EGF receptor signaling decreases the number of adenomas (polyps) by 90 percent.

So for a small polyp to progress, “it’s very important to have intact EGF receptor signaling,” Coffey says. And several targeted

cancer therapies – Erbitux (cetuximab), Tarceva (erlotinib) and Iressa (gefitinib) – now exploit and try to inhibit EGF receptor signaling to stall the progression of cancer.

But these later genetic events occur in only certain fractions of tumors, says Beauchamp. So while knowing which of these mutations a patient has might not predict whether they develop cancer initially, these genetic signposts may be particularly useful in determining prognosis and predicting response to treatment.

For example, “patients with activated MAP kinase pathway – like those who have mutations in K-ras or B-raf – are unlikely to respond to therapies targeting the EGF receptor,” he says.

Recently, Beauchamp’s lab has identified a set of genes that seem to predict a poorer prognosis in colon cancer. This may eventually help clinicians choose the appropriate course of action for patients based on the gene expression “signatures” found in their tumors.

While these mutations are not currently tested for as a part of standard cancer care, identifying these genetic signatures could help predict which tumors are most likely to progress, which patients are at highest risk of recurrence and metastasis, and which patients will respond to particular therapies.

“Ultimately, this will lead to more individualized therapy for cancer patients,” says Beauchamp.

### Most likely...to metastasize

Once a polyp has developed – and if it is not removed – that polyp will likely develop into a carcinoma, a malignant tumor of the epithelium, with the potential to spread.

This transition – from a benign polyp to malignant cancer – is often associated with mutations in the p53 gene, another tumor suppressor. The protein it encodes has many nicknames – “guardian of the genome,” “the guardian angel gene,” and the “master watchman” – reflecting its importance in preventing potentially cancer-causing mutations.

About 50 percent of colon cancers have a mutation in p53, which causes the protein to lose its cancer-fighting function.

“If you lose p53, you lose the ability of the cell to undergo programmed cell death in response to DNA damage. So these cells don’t commit ‘suicide’ when they’re supposed to,” says Beauchamp.

“It’s not clear that loss of p53 is the event that tips these tumors into becoming invasive carcinomas, but it certainly contributes in some of them.”

The genetic alterations that propel cancer cells to invade and metastasize to distant tissues – the aspect of cancer that causes most cancer deaths – remain perhaps the biggest question in cancer biology.

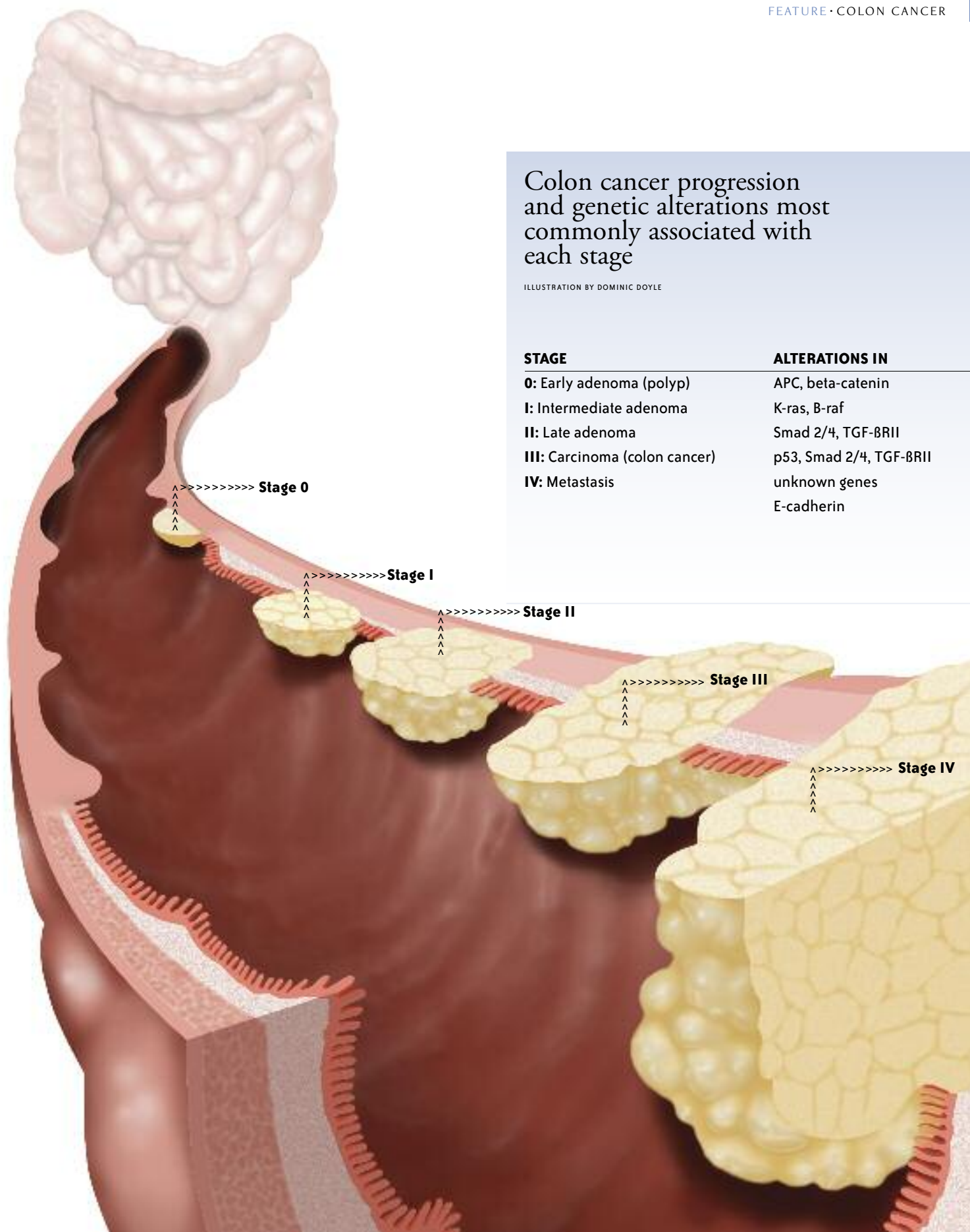
The process requires that the tumor cells, which are at first sequestered in their tissue of origin, to break free of the molecular bonds that hold them there. One class of bond-forming proteins is the cadherins. Cadherins reside on the surface of cells, and E-cadherin (the “E” is for “epithelial”) molecules on adjacent cells “zipper up” and bind those cells together while maintaining normal polarity. Loss of E-cadherin function seems to be a required for a cancer to become invasive.



## Colon cancer progression and genetic alterations most commonly associated with each stage

ILLUSTRATION BY DOMINIC DOYLE

STAGE	ALTERATIONS IN
<b>0:</b> Early adenoma (polyp)	APC, beta-catenin
<b>I:</b> Intermediate adenoma	K-ras, B-raf
<b>II:</b> Late adenoma	Smad 2/4, TGF- $\beta$ RII
<b>III:</b> Carcinoma (colon cancer)	p53, Smad 2/4, TGF- $\beta$ RII
<b>IV:</b> Metastasis	unknown genes E-cadherin





14 The genetic alterations that propel cancer cells to invade and metastasize to distant tissues – the aspect of cancer that causes most cancer deaths – remain perhaps the biggest question in cancer biology.



## My Colonoscopy

*(Or why I'll never drink ginger ale again)*

BY WAYNE WOOD

As an article title, I'm the first to admit that "My Colonoscopy" doesn't have the got-to-read-it gravitational pull of, say "My Six Months of Captivity in the Amazonian Jungle," "My Experiences (Along with Paris Hilton) on a Nude Pirate Ship," or even "My Recipe for Cranberry Apple Crumble."

Beauchamp is currently leading a screen for compounds that restore E-cadherin function, in hopes of finding ways to reverse the epithelial-mesenchymal transition that contributes to metastasis.

"In epithelial cells, loss of E-cadherin or E-cadherin function marks the transition to metastasis," explains Albert Reynolds, Ph.D., a professor of Cancer Biology at Vanderbilt. "Before that happens, you can just take the tumor out and people are fine. After that, it's pretty rough going."

About 20 years ago, Reynolds discovered a partner of E-cadherin, a protein called p120-catenin, a molecular "cousin" to beta-catenin. The protein binds to the tail of the E-cadherin protein, which dangles into the interior of the cell, and regulates cadherin function.

His lab recently showed that p120's role is much broader than simply regulating cadherin function. They found that p120 is actually at the nexus of several different signaling systems involved in cancer progression.

"p120 is central, not only to cadherin signaling, but to crosstalk between different systems in the cell that regulate motility, cell-cell adhesion, and growth," Reynolds says.

Reynolds and colleagues are now working on mouse models to evaluate the effects of p120 loss in colon and breast cancers. While clinical application of the findings are yet to be realized, Reynolds predicts that drugs that target p120, or other components of this complex pathway, could be useful inhibitors of metastasis. In fact, says Reynolds, "everything about the cadherin complex has been implicated in cancer."

Still, there are a couple of points to be made in defense of the whole colonoscopy thing.

Point 1: A colonoscopy requires 24 hours or so of less-than-totally-comfortable (though certainly not excruciating) living.

Point 2: At the end, you will likely hear that you don't have colon cancer; although

Point 2 (a): If you do have cancer or a pre-cancerous polyp, it will likely be far more treatable now than if you had put off your colonoscopy.

So, to sum up, you invest 24 hours of relatively minor discomfort in order to either get very good news—and, let's face it, "You don't have cancer" is pretty darn good news—or at least give yourself the best chance of dealing with whatever else as early as possible.

The downside is that you may never think of chicken broth or ginger ale in quite the same way.

At least that was my experience. You have probably heard that in order to have your colon completely examined, it's necessary for your colon not to have in it what your colon normally has in it, if you get my drift.

So in order to clear the decks, so to speak, you will need to take a product such as GoLYTELY, which, I hope I can say without being sued, is one of the most misleadingly named products in history. Seriously, it's as if somebody went around marketing bark mulch under the brand name SweetNTASTYEE. GoLYTELY is a class of product that falls under the snappy sobriquet "bowel evacuant." I'll bet your sphincter tightened as you read those words.

Since on the day before a colonoscopy, you are limited to clear liquids after noon, I stocked up on ginger ale and chicken broth. I had the broth for both lunch and dinner that day, and mixed the ginger ale with the



### Reply hazy...

While we now know a lot about the genetic alterations involved in colon cancer, a vast frontier remains unexplored.

For example, researchers are fairly certain that cancer usually starts in one cell. But what cell? And where is this cell located within the colonic crypt?

Mature epithelial cells reside at the “peaks” of the colonic crypts, while proposed stem cells are tucked away at the base of the deep “valleys” of the crypts.

If the cancer’s origin is in the colon epithelium, which cell is it that accumulates the cancer-causing mutations? Are the ever-elusive “stem cells” the source?

“There’s a controversy in the field,” Coffey explains. “Does colon cancer go top-down (from mature epithelium to stem cells) or bottom-up?”

While some cancer biologists think it proceeds top-down with the initiating event in the mature epithelial cells, Coffey thinks that it is more likely that colon cancer starts at the bottom—in the stem cells sequestered at the base of the colonic crypts.

Using genetically engineered mice and techniques that can alter the expression of cancer-promoting genes in specific parts of the colonic crypt, Coffey hopes to answer that question.

“It is such a fundamentally important biological question,” he says, “but nobody has done this yet ...because nobody has had the tools to do it.”

Now Coffey thinks it is possible to find the exact cells in which colon cancer originates. This information could usher in a new way of thinking about colon cancer development and therapy.

Additionally, non-epithelial cells may be an overlooked contributor. But Hal Moses, M.D., Vanderbilt-Ingram’s founding director, and colleagues have shown in mice that disrupting TGF- $\beta$  signaling in the surrounding, supportive cells—called stromal cells—can initiate a cancer in the adjacent epithelium of the prostate and forestomach. The findings highlight the importance of the tumor “microenvironment,” an aspect that remains a major area of exploration for Vanderbilt-Ingram researchers.

For now, the best defense against this disease is screening and early detection. The current recommended age for having a screening colonoscopy is 50. If a patient has a family history of colon cancer or symptoms suggestive of polyps or cancer, a screening colonoscopy should be done earlier.

Although it is the best we have, Beauchamp knows that even strict compliance with colonoscopy screening recommendations may not catch everyone, especially those who are young and asymptomatic.

Patients must be proactive and advocate for themselves, he says. Tell your doctor if you’re experiencing symptoms and—especially if you experience bleeding—ask for a colonoscopy if one is not offered.

“Anybody who has rectal bleeding has to be worked up for the possibility of colorectal cancer. Odds are they won’t have it, but you can’t tell...until you actually check.”



web link

More information about Vanderbilt-Ingram’s gastrointestinal cancer research at: [www.vicc.org/research/programs/gi.php](http://www.vicc.org/research/programs/gi.php)

GoLYTELY solution to make it more palatable. The directions say to drink an 8-ounce glass of the mixture every 15 minutes until a whole gallon is gone.

I used to really like ginger ale.

There is nothing quite as droll as the printed patient instructions that accompany this preparation phase. “You will need to plan on being near a bathroom for the entire evening,” one laconically notes.

Yeah, I’d say my experience was consistent with that bit of advice.

One overlooked advantage of colonoscopy prep, though, is that you can take care of a lot of reading that you’ve been putting off. I discovered this when a friend of mine confessed that he had been putting off reading a book I had written until his colonoscopy.

“Your book is great colonoscopy reading,” he said afterward. I’m considering using that as a cover blurb on the second printing.

Movie viewing is more problematic. I seem to recall that my wife Sharon and I were trying to watch a movie on DVD that night and that the pause button got quite a workout.

The next day, Sharon and I made our way to the Gastroenterology Clinic at Vanderbilt, and I met the cheerful staff of the clinic. One of the staffers, it turned out, was a former E.R. nurse with whom I had often talked by phone but had never met.

“It’s so nice to put a face with a voice,” she said.

“That’s not all you’re going to be putting with my voice,” I told her.

An IV line in my arm fed an anesthetic, I rolled onto my side when I was told, and, honestly, that’s about all I remember. I know that for television reporting purposes, Katie Couric was fully conscious when she had her famous nationally-televised colonoscopy several years ago. I was not. If you get a choice, I recommend

my method over Katie’s.

Pretty much the next thing I remember was Sharon’s lovely face in the recovery room as I woke up. The gastroenterologist who had performed the colonoscopy came in to tell us that everything looked fine and that I wouldn’t have to do this again for 10 years. Sharon drove me home—it’s a requirement that a patient getting a colonoscopy have a designated driver—and I took it easy the rest of the day.

I wouldn’t say this was my favorite couple of days in my life, but really it was no big deal. And in return I found out that my colon was fine, which—stop me if you’ve heard this before—is really good news.

There was one major downside, though. I haven’t had any ginger ale since.







the  
gift  
of friendship

Oncology nurses provide more  
than just medicine

*By Dagny Stuart | Illustration by Scott Laumann*





# Betty Eaves knew she had heard that voice before.

Above the din of the bustling outpatient cancer clinic where Eaves was having lab work done, a reassuring voice she had previously heard only over the phone caught her attention.

Shocked by her diagnosis of lung cancer in January 2008, Eaves had made numerous calls to Vanderbilt-Ingram Cancer Center oncologist Alan Sandler's office for guidance during her treatments.

Even her 20 years in emergency management – and a high-pressure job as an assistant to then Speaker of the Tennessee House of Representatives, Ned McWherter, who later became Tennessee's governor – hadn't prepared her for the painful and frightening side effects of her cancer treatments.

"I panicked a couple of times," said Eaves. "I was in pain and didn't know why I was hurting."

That voice heard outside the lab had calmed her fears during those frantic phone calls.

Eaves soon identified the source of that voice and hurried over to the information desk to introduce herself to Lynetha Verge, the oncology nurse whose humor and quiet assurance have helped so many Vanderbilt-Ingram cancer patients. The relationship that started during those telephone consultations soon blossomed into a real friendship that has endured.

"Our conversations have turned into everyday chit chat and girl talk," Verge explained with a smile. "We talk about our favorite kind of wines or something that happened during a shopping trip. I think when we have our girl talk that helps her feel normal and that she's not just her cancer."

Verge is just one of the many oncology nurses at Vanderbilt-Ingram who forge strong, intimate and often lasting bonds with their patients.

Growing up in Lexington, Tenn., there was never any doubt that Verge would follow in the footsteps of her grandmother who, at age 71, still works as a nurse caring for patients.

"I grew up watching her go to work and, of course, she was dressed in her white dress and white stockings and that stiff white cap. I was going to be a nurse just like her."

Her grandfather's cancer diagnosis led to her nursing specialty.

"My grandfather raised me, and he died from lung cancer," Verge explained. "I just knew when I graduated from Methodist School of Nursing in Memphis that oncology was what I wanted to do."

For 10 years, Verge has specialized in caring for cancer patients – moving from floor nursing to the stem cell transplant clinic. She has first-hand knowledge of what families there are experiencing after her mother developed aplastic anemia and needed a stem cell transplant. Verge was the best match, so the two women traveled to Duke University Medical Center where Lynetha donated her own stem cells to try to save her mother's life. A month later, her mother developed graft-versus-host disease and died. Despite the outcome, Verge feels blessed to have participated in the medical quest to save her mother, calling it a wonderful experience that has reinforced her special kinship with families in the transplant clinic.

"It's like a big family because you see the transplant patients daily," she said. "I've always enjoyed that part of nursing, knowing that I'm going to see a patient again on a regular basis. We cry together. We share the family births and the weddings and anniversaries. They get to know about my family, and they ask about my children."





During her battle with lung cancer, Betty Eaves (left) developed a lasting friendship with oncology nurse Lynetha Verge, R.N., O.C.N., (right).

JOE HOWELL



Verge now works in the outpatient clinic, helping lung cancer patients like Betty Eaves, who considers the nurse her partner in the fight against cancer.

"She is my rock," Eaves explained. "She is the one who lets me know what I need to know. You can ask questions that you normally wouldn't ask someone you don't feel close to. I've never had that bond before. It feels really good, and it feels safe. It's very much a part of what makes you feel better and work harder toward your goal of getting well."

## A profession in peril?

The close relationship that develops between cancer patients and their nurses is just one of the reasons so many nurses choose to specialize in oncology. But there is a storm looming on the horizon for oncology patients – a projected shortage of oncology nurses like Verge to care for the coming wave of 80 million baby boomers whose advancing age will put them at increased risk for cancer.

"Our projections show that when we reach 2015, the nursing workforce – which has been growing at a very slow rate – will stop growing just as demand is increasing at a strong clip," said Peter Buerhaus, Ph.D., R.N., director of the Center for Interdisciplinary Health Workforce Studies.

In the meantime, the existing nursing workforce will be retiring in large numbers throughout the decade, leading to very large

shortages in the latter part of the next decade and reaching a deficit of 285,000 registered nurses by 2020, Buerhaus said.

"That is almost three times larger than any shortage we've experienced in the last 50 years. I worry deeply about that because a shortage of this magnitude could mean that the lights will turn off on some nursing units," Buerhaus predicted. "It will cause hospitals to reduce hours of operation for certain services. Quality of care will be at risk because there will not be enough staff. Safety will be at risk, and it gets worse."

By the year 2025, Buerhaus predicts the shortage will grow to 500,000 – a shortage so large that it could become a major economic issue for the nation.



## 20 Helping Hands

While Janie Hughes was undergoing treatment for multiple myeloma – a cancer of the antibody-producing plasma cells of the blood – she spent a great deal of time watching other Vanderbilt-Ingram patients struggle with financial issues, in addition to their cancer. She and her husband, Bob, wanted to make a donation that would be meaningful.

“Bob Hughes told us he didn’t want to build a memorial wall with their name on it, he wanted to use the funds to help other people,” remembered Carey Clifton, a nurse practitioner in the stem cell transplant long-term care clinic. “We started talking about people whose transplants were delayed because they could not afford preventive dental treatment or necessary repairs prior to transplant.”

Cancer patients often experience tooth or gum problems as a side effect of cancer treatment. They must have dental problems fixed prior to transplant because those problems could cause potentially life-threatening infections. Private insurance doesn’t always cover those costs.

“Janie thought there was no justice in the world if people couldn’t get their cure because they couldn’t pay for the dentist,” Clifton said. “If people needed dentures, she wanted them to get dentures.”

The Hughes family discussed the issue with another couple, Chad and Haley Welch, while Chad was undergoing treatment for acute myelogenous leukemia. Friends of Chad had already started “Team Chad,” a fundraising organization to aid research in leukemia and lymphoma.

Together, the families decided to help launch the Hematology Helping Hands Fund, dedicated to providing financial support to cancer patients, as well as cancer research.

“The primary doctor for Chad and Janie was Dr. Madan Jagasia at Vanderbilt-Ingram. I believe Dr. Jagasia can move mountains, and I will give him every cent that I have for this cause because I trust him that much,” said Haley Welch. “We’ve seen

people die because they didn’t have insurance to pay the thousands and thousands of dollars it costs to do a stem cell transplant. It was heartbreaking, and it is not acceptable.”

The Hematology Helping Hands Fund, administered through the Development Office of Vanderbilt-Ingram, provides funds for direct patient care, as well as research.

While both Chad Welch and Janie Hughes died from their cancer, their families continue to raise funds to fight the disease.

“While Chad was alive, we were involved in ‘Light the Night,’ the annual fundraiser for the Leukemia and Lymphoma Society,” said Haley. “After Chad died, it was so cathartic for his friends and family to continue to raise money. The question was, ‘where do we put this money?’”

“We wanted to focus on something that had impacted us. We weren’t sure how and where to focus our efforts, and Carey Clifton stepped in and told us there was a way to do this.”

Clifton says the Helping Hands Fund is the fulfillment of her promise to the two families.

“Part of the money is used for research projects, and the rest goes to fulfill their wishes, helping patients in little ways to make a huge difference,” said Clifton. “It made me feel great knowing that these patients, even at the most stressful point in their lives, formed such a strong bond with other families and wanted to help others. To know that we’ve been able to help make that happen warms your heart. It makes what we do worthwhile.”



### web link

If you are interested in making a donation to the Helping Hands Fund, visit [www.vicc.org/giving](http://www.vicc.org/giving) and designate Helping Hands Fund in the comments box.

More information about Team Chad at: [www.teamchad.us/index.htm](http://www.teamchad.us/index.htm)

Members of Team Chad gathered for a group photo before the 2008 Country Music Half Marathon. Photo courtesy of Jeff and Erin Andrews.



## The close relationship that develops between cancer patients and their nurses is just one of the reasons so many nurses choose to specialize in oncology.

“Such a future doesn’t have to evolve,” he said. “There is time to avert such a shortage, but we need to get moving, now!”

Buerhaus says recently published research studies provide convincing evidence that nursing staffing levels have a direct impact on the quality of medical care.

“Taken together the evidence is fairly clear that low staffing is associated with increased risk of urinary tract infections, pressure ulcers, medication mistakes, falls with injuries, GI bleeding, pneumonia, blood stream infections and probably another half-dozen or more negative outcomes,” Buerhaus said.

Physicians specializing in cancer also recognize that having specially trained oncology nurses has a positive impact on patient outcomes.

“From data we collected in 2000, we asked oncologists if they see a difference in the quality of care related to nurses who have a specialty in oncology or are in oncology-specific units,” Buerhaus explained. “They were aware of that difference, and they valued that difference.”

### The biggest gift

Carey Clifton ended up in oncology by accident – it was the only available nursing job at Vanderbilt that matched her qualifications. But that unplanned exposure to cancer patients changed her life.

“It just takes a day with these people to know that it’s a special area of medicine,” said Clifton, who is now a nurse practitioner working in the Vanderbilt-Ingram stem cell transplant clinic.

“When you read through these records that are so complicated, it’s very overwhelming,” Clifton said. “But when you sit down and meet the patients and their parents and siblings, they’re real people who are fighting for their lives, so it’s worth the fight to help them, even if the cure is a long shot. It’s worth it to help them along that journey.”

A long shot is exactly what Chad Welch faced. The Nashville man was just 27 when he was diagnosed with acute myelogenous leukemia. He and wife Haley had only been married for two years when they received the diagnosis.

“I knew it was bad from the beginning and that we were up against a battle,” said Haley Welch.

One of the first people the Welches met when they were admitted to Vanderbilt University Medical Center was floor nurse Leslie Wyttenbach Goebel.

“I remember walking in and seeing Leslie’s smiling face. She knew it was the worst day of our lives, but she just made us feel like, ‘Okay, we can get through this. We can get through today,’” Haley remembered.

During the months Chad spent in the hospital, another oncology nurse cared for him in the overnight hours.

“When I think about someone who has a calling, I think about Rebecca Bice who works the night shift as a charge nurse on the stem cell transplant floor,” Haley explained. “That may be the toughest job I can think of, and she does it with such a pure heart and such joy.

“I spent every night in the hospital with Chad, and on the nights Rebecca was there I could sleep. That was the biggest gift she

Haley Welch describes nurses Leslie Wyttenbach Goebel (left) and Rebecca Bice (right) as her “angels.”



JOE HOWELL





Nurse practitioner Carey Clifton (right) helped Chad and wife Haley Welch (left) and another family establish the “Hematology Helping Hands Fund,” which provides financial support to cancer patients and cancer research.

gave me because I knew no matter what happened, she would take care of Chad and love him the way I did.”

Welch calls Goebel and Bice her “angels” who helped the couple during the two years of Chad’s medical care, which included induction chemotherapy and a stem cell transplant.

“When you’re there through the hardest time in your life, every single day, you live and breathe it – and they live and breathe it with you,” Haley said. “They asked us what we needed, ‘what can we do for you because we know how hard this is?’

“It was nice to feel that sort of connection with them.”

Haley also appreciated the honesty of the nursing team, including Carey Clifton, who cared for the couple in the long-term care stem cell transplant clinic.

“When I asked some very serious questions about Chad’s chances, they would tell me the truth,” said Haley. “They wouldn’t sugar-coat anything, and I appreciated that.”

Helping families through such emotionally wrenching times can be difficult for oncology nurses, who must learn to cope with their own feelings.

“It’s tough. When they’re happy, we’re happy. When they cry, we cry and that helps us get through it,” said Lynetha Verge. “I think our patients like it when we show emotion. We’re not steel. We feel things, too.”

Verge says learning to share the emotional highs and lows that come with cancer care helps oncology nurses stay in the field.

In the Vanderbilt-Ingram chemotherapy infusion clinic, nurses sing, wear funny hats and play kazoos to help patients celebrate their final day of chemotherapy. Oncology nurses also mourn alongside families when patients succumb to their cancer.

Haley Welch says she appreciated the pure emotions exhibited by all of the nurses who cared for Chad, who finally passed away in June 2007, at age 30.

“The nurses became family. They saved me, in every sense of the word.” ☺



web link

More information about the Oncology Nursing Society at: [www.ons.org](http://www.ons.org)



# Leading the Way

Expanding and remodeling the Henry-Joyce Cancer Clinic at Vanderbilt-Ingram Cancer Center is a massive job. One of the overseers of that project is Jennifer Woods, R.N., B.S.N., MBA, oncology nurse and manager of the Cancer Patient Care Center.

"I have the contractors on speed-dial," Woods laughed. "I love working on big projects and focusing on quality and how we can do things better."

That includes introducing a pager system for patients and family members, so they can move around the Medical Center and still be notified when it's time for their appointment.

Woods has been an oncology nurse for 20 years, including a stint in the bone marrow transplant unit at Vanderbilt University Medical Center, before she moved into a management role. She is now undertaking a leadership position with the Middle Tennessee Chapter of the Oncology Nursing Society. As of January 2009, Woods is serving as president of the organization, which boasts 130 active members.

The national Oncology Nursing Society provides nurses with educational and certification programs. But it is the opportunity to join other oncology nurses to influence public health care policy at a regional and national level that Woods finds most intriguing.

"One of the legislative measures we are supporting would allow health care providers to bill insurance companies for one hour of patient education," Woods explained. "We can actually decrease the cost of care by allowing nurses to give patients proper education about their conditions, medications and lifestyle issues. If we could bill for that hour we could increase our resources, and in the long run it will reduce health care costs."

Woods says oncology nurses also can make a difference in cancer prevention by advocating for coverage of preventive cancer screening, including more opportunities for colon cancer tests.

"Colon cancer is a very curable and treatable disease if you catch it early, but we need to find a way to offer affordable screening to more people," Woods said.

Woods believes nurses can achieve great things by banding together.

"Most nurses have no idea what goes on politically, and my interest as president is to bring awareness, to let them know who is making these decisions and why they're making these decisions.

"If nurses want to have a say in how things in the health care industry are done, we need to come together to be heard. I think nurses have been a sleeping giant long enough. We have a big voice, and we need to use it."

— by Dagny Stuart

Jennifer Woods, R.N., B.S.N., MBA, oncology nurse and manager of the Cancer Patient Care Center at Vanderbilt-Ingram, recently became president of the Middle Tennessee Chapter of the Oncology Nursing Society.



JOE HOWELL



THE  
STRANGE  
CASE OF



# TGF-*β*

*By Melissa Marino*



## He refers to it as Jekyll and Hyde.

The protein to which Hal Moses, M.D., has dedicated nearly three decades of research – transforming growth factor-beta (TGF- $\beta$ ) – has two personalities.

In normal cells, TGF- $\beta$ 's beneficial “Dr. Jekyll” persona inhibits cell growth and suppresses tumor formation. But sometime during the development of cancer, the protein's good side is replaced by its more sinister tumor-promoting “Mr. Hyde” personality.

And like the good Dr. Jekyll's transformation into the depraved Mr. Hyde, TGF- $\beta$ 's role reversal also requires a mysterious set of biological “potions.”

These features have made TGF- $\beta$  and its large molecular family promising targets for cancer therapy. But even now, some 30 years after it was first identified, TGF- $\beta$  still withholds many of its secrets.

Moses, the founding director of the Vanderbilt-Ingram Cancer Center and the current director of the T.J. Martell Foundation's Frances Williams Preston Laboratories, has made it his life's work to solve the riddle of TGF- $\beta$  function, in hopes of finding new ways to treat cancer.

### Mr. Hyde

Moses' interest in cancer biology was born during his early career at Vanderbilt. A 1962 graduate of the Vanderbilt University School of Medicine, Moses had returned to Vanderbilt in

1968 after a three-year research stint at the National Institutes of Health. But the heavy clinical load at Vanderbilt soon prompted Moses to head to the Mayo Clinic in Rochester, Minn., to concentrate on his true passion – research.

In the early 1980s, Moses was investigating how normal cells could be “transformed” into malignant ones. He was specifically searching for factors that could give cells the ability to grow when suspended in a semi-solid agar (a jelly-like substance used for growing cells in culture).

While most normal cells will not grow in this environment, “transformed” (malignant) cells will, forming tiny tumor-like cell clusters in the agar. This growth, Moses says, “was and still is the best *in vitro* correlate of tumorigenicity.”

In 1978, researchers at the National Cancer Institute had isolated and partially purified a factor secreted by cells that had been transformed by a cancer-causing virus. The factor bound epidermal growth factor (EGF) receptors – major cell growth regulators. The factor was dubbed “transforming growth factor,” and suggested to have the ability to turn normal cells malignant.

In 1981, Moses' lab began striking the first chinks in the factor's identity, showing that this one factor was actually two – that its ability to bind EGF receptors was separate from its ability to turn normal cells cancerous.

“We were slow getting (the results) out because we were very uncertain about it,” Moses says. “But even so, we were the first group to report on a transforming growth factor that does not bind to the EGF receptor.”

Moses' close competitors at the NCI – led by Michael Sporn, M.D., and Anita Roberts, Ph.D. – weren't far behind. In September that same year, the NCI group reported similar results, leading to the differentiation of a separate “TGF- $\alpha$ ” (the EGF receptor-binding activity) from “TGF- $\beta$ ” (the tumor-promoting activity).

Thus the TGF- $\beta$  field was born. And the race to uncover its secrets spawned a career-long friendship and collegial competition between Moses and Roberts. Shortly before Roberts died in 2006, she and Moses completed a history of the TGF- $\beta$  field – a culmination of the work to which they and others have devoted their careers.

The early years were productive. Moses' lab found TGF- $\beta$  activity in mouse embryos (an indication of its crucial role in development), and identified receptors through which TGF- $\beta$  acts to regulate cell growth and division. Moses also identified an easily accessible and abundant source of the protein in blood platelets, those tiny cells that help blood clot. Platelets, Moses noted, are now the source of much of the TGF- $\beta$  on the world market.

### Dr. Jekyll

But soon, Moses noticed something unexpected from a supposed tumor-promoting factor. The TGF- $\beta$  they had isolated from platelets seemed to be inhibiting the growth and multiplication of certain types of cells in culture.

This unanticipated inhibitory activity was creating confusion in the Roberts lab too. They had also been noticing a growth defi-

ciency in some cancer cells treated with TGF- $\beta$ , but assumed that the decreased cell growth was due to impurities in the TGF- $\beta$  preparation.

In the spring of 1984, Moses presented his results on this growth inhibition at a national meeting, and Roberts listened as he presented his data.

"I felt the blood drain from my body, because we were very competitive in those days," she said in a 2004 video interview. She hurried out of the auditorium to phone the lab. "I said 'our experiments aren't wrong, it's growth inhibition!'" she relayed to her colleagues back at the NCI.

"So we had found – sort of serendipitously – that it would inhibit growth," Moses recalled. "It's the sort of moment you live for. Science can be very frustrating. You can go for months with a lot of frustration and no reward. But a moment like that will carry you for a few years."

Moses returned to Vanderbilt in 1985. And in 1993, with the new influx of support from the T. J. Martell Foundation, he and his Vanderbilt colleagues were able to create the animal models they needed to study TGF- $\beta$ 's *in vivo* roles.

"(Martell's) support was critical for us to be able to do the mouse models," Moses says. His lab was able to create mice with TGF- $\beta$  expression altered only in specific sets of cells – a crucial technique for defining the protein's biological functions.

In one study, his group overexpressed TGF- $\beta$  in the mammary glands of mice, showing that this amped-up TGF- $\beta$  activity could slow development of mammary tumors.

After years of research showing TGF- $\beta$ 's growth inhibitory role in cultured cells, this work provided some of the first solid evidence of TGF- $\beta$ 's tumor-suppressing ability in animals.

These animal studies, "contributed to a large body of data indicating that TGF- $\beta$  signaling is tumor suppressive," Moses says.

Moses (seated far right) with some of the other early contributors to the TGF- $\beta$  field at a 2006 conference. Seated: Rik Derynck (left) and Anita Roberts (right). Standing: Michael Sporn (left) and Joan Massagué (right).



"It's likely from what we know now that it is one of the major tumor suppressor pathways."

Mounting evidence of mutations in TGF- $\beta$ , its receptors, and its extended family of signaling molecules suggests that errors in the TGF- $\beta$  "superfamily" might be an instigating factor for various cancer types – including colon, breast and pancreatic cancers.

"In fact, for normal cells to become cancer cells, there has to be an impairment of this signaling pathway," Moses says.

### The transformation

In normal cells, TGF- $\beta$ 's "Dr. Jekyll" personality dominates, restricting cell growth, differentiation and cell death. This is key to keeping normal developmental processes and the body's repair mechanisms in check.

But sometime during the early stages of cancer, TGF- $\beta$  signaling is lost – typically because of a mutation in some component of the system (e.g., TGF- $\beta$  receptors, or the downstream "second messengers" that carry the TGF- $\beta$  signal to the cell's nucleus). These changes coincide with TGF- $\beta$ 's transformation into its tumor-promoting alter ego.

"The current dogma is that early in tumor formation and the initiation of cancers, TGF- $\beta$  remains tumor suppressive. Then later it changes to Mr. Hyde to promote tumor growth and metastasis," Moses explains.

The triggers for this personality switch are unclear. But recently, Moses and colleagues found an important role for a type of bone marrow-derived immune cells, called myeloid immune suppressor cells (MISCs), in this switch.

Moses and Vanderbilt-Ingram colleague Li Yang, Ph.D., deleted the gene encoding a TGF- $\beta$  receptor in a mouse model of breast cancer, disrupting TGF- $\beta$  signaling in the breast cancer cells.

The tumors of these mice contained a significantly higher number of MISCs than tumors from mice with a functional TGF- $\beta$  receptor. This increased recruitment of MISCs to the tumor was sparked by the increased production of certain chemokines – signaling chemicals that influence immune cell behavior – by the tumor cells. The studies suggested that TGF- $\beta$  signaling normally suppresses important chemokines.

"So if you lose the signaling in cancer cells, the tumor cells produce more chemokines, and this brings in more bone marrow-derived cells, which promotes metastasis," says Moses. These cells, he suggests, may be "the answer to the TGF- $\beta$  paradox."

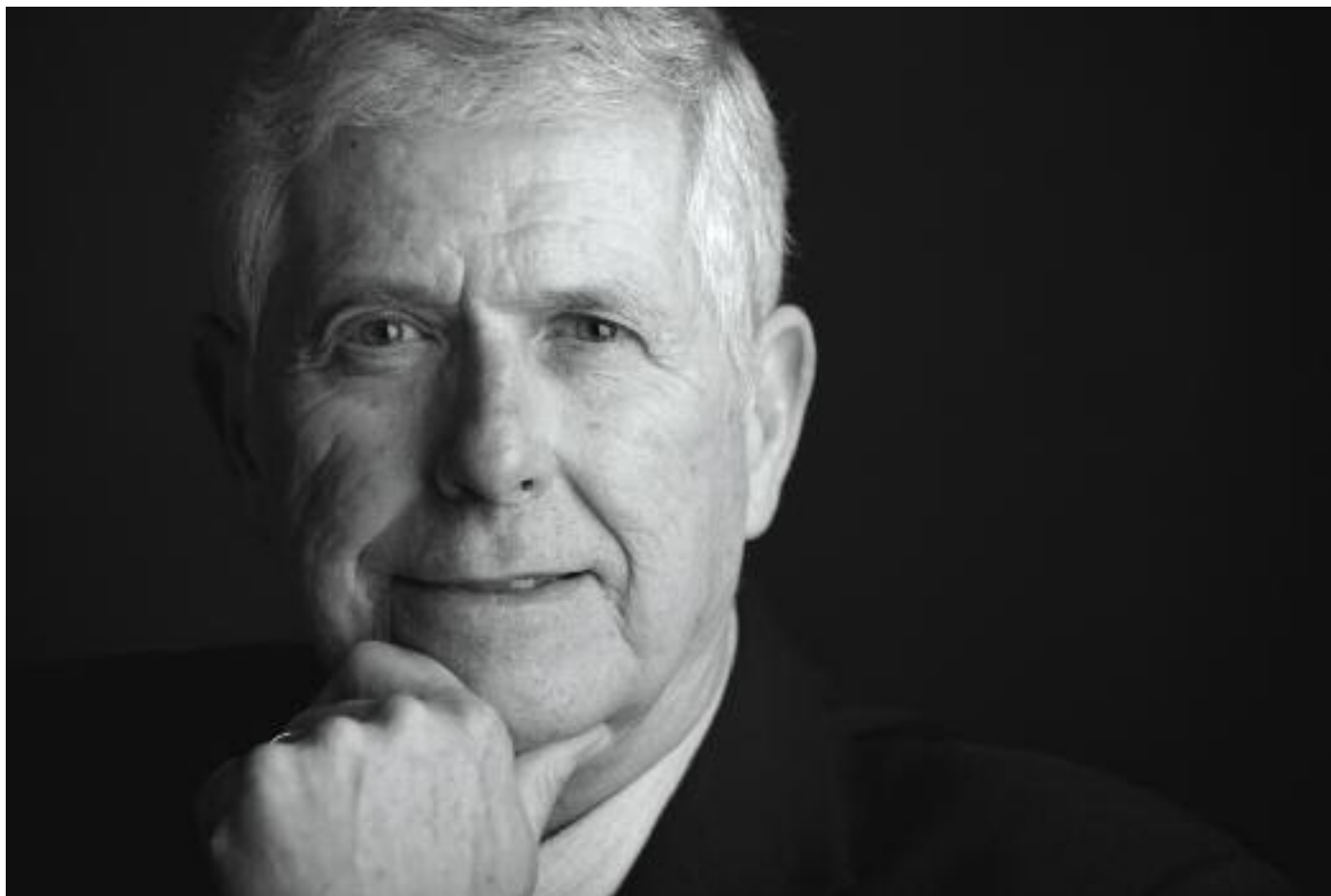
Because blocking the interaction between the chemokine and its receptor inhibits the recruitment of MISCs, these immune cells or the chemokine signaling involved might represent useful therapeutic targets for inhibiting metastasis.

### Beware of neighbors

The importance of these cells in cancer progression highlights another new research direction for the Moses lab: the tumor microenvironment, or stroma.

The stroma is a supportive meshwork of proteins and polymers and the cells that secrete these components, called fibroblasts.





JOE HOWELL

Moses' lab is now working to understand the interactions between the stroma and tumors.

"We've become interested in the tumor microenvironment because TGF- $\beta$  signaling is a major regulator of what goes on in the microenvironment of cancer," he says.

In a mouse model, Moses' group has shown that disrupting TGF- $\beta$  signaling selectively in fibroblasts can initiate carcinomas – cancers that arise from epithelial cells that line body cavities – in the prostate and forestomach (an organ similar to the esophagus in humans).

"To my knowledge, this is the first demonstration of the development of a carcinoma with the initiating genetic lesion in stromal cells," Moses says.

The importance of this previously overlooked factor – the biological "stuff" that surrounds the tumor cells – is changing the way cancer researchers think about treating cancer.

"For many decades we have focused on just treating cancer cells, expecting that the host (stromal) cells are just bystanders," Moses says. "We now know that is not the case, that invasive cancer is like an organ."

This "organ" called cancer is not only composed of cancer cells, but the fibroblasts and the bone-marrow derived (immune) cells that help the cancer invade and grow, Moses explained. And TGF- $\beta$  appears to have an important role in how this "organ" interacts with its microenvironment.

TGF- $\beta$ 's ability to both promote and suppress tumor growth makes this signaling pathway an attractive – but risky – therapeutic target. Inhibiting TGF- $\beta$  signaling at the wrong time or in the wrong cells might actually promote the cancer's spread.

Still plugging away at the complex system, Moses sees the TGF- $\beta$  field as full of potential and opportunity. For one, the TGF- $\beta$  "superfamily" is incredibly complex, containing nearly 40 ligands, 12 receptors, and dozens of downstream signaling intermediates. Also, the range of biological functions that involve TGF- $\beta$  continues to grow broader.

This complexity has helped keep TGF- $\beta$  research going strong for three decades.

"It's never been easy," he says. "It's always been a difficult pathway to study. But when many other areas have received decreased interest and funding, TGF- $\beta$  continues to become more and more complicated."

That leaves a lot of work yet to do. But Moses is undeterred. After stepping down as the Cancer Center's founding director in 2004, Moses returned with renewed energy to peeling away the layers that conceal TGF- $\beta$ 's many identities and functions.

Now focused on understanding how TGF- $\beta$  enhances invasion and metastasis, he hopes that the discoveries his team makes will lead to new therapeutic targets for preventing or limiting metastasis.

And while proud of his accomplishments in establishing and leading the Cancer Center, Moses can't get away from his calling, his inner detective.

"I've done a lot in terms of administration, but my real love has always been my research program." ◉

*Moses is also the Hortense B. Ingram Professor of Molecular Oncology; professor of Cancer Biology; professor of Pathology; and professor of Medicine.*

# A Marriage of Music and Medicine

By Cynthia Floyd Manley

**A**s the crow flies, the distance between the scientists at Vanderbilt and the artists on Nashville's world-famous Music Row can be measured in yards.

But in the early 1990s, it might as well have been light years. The two didn't know each other, and they certainly didn't grasp the potential for the difference they could make if they came together with a common purpose.

One woman changed that. Frances Williams Preston, a music industry icon known for her generous spirit and unrivaled tenacity, was approached to be the honoree at the T.J. Martell Foundation's annual fund-raising gala in New York City. The Nashville native saw it as an opportunity to create something special in her hometown.

"I told them I would do it so long as some of the funds raised were used to support cancer research right here at Vanderbilt," Preston recalls.

The result was the Nashville division of the music industry-based charity, its Frances Williams Preston Laboratories and a new Cancer Center at Vanderbilt. The Center (later the Vanderbilt-Ingram Cancer Center) would develop into one of the strongest cancer research programs anywhere.

Starting with an initial investment of \$1 million, the commitment for these "laboratories without walls" was a cornerstone of the new Center. Over 15 years, the Foundation has contributed more than \$15 million for innovative research at Vanderbilt-Ingram. At any one time, about 20 investigators are directly supported by the Foundation, but virtually every scientist in the Center benefits from its impact.

"Our philosophy from the very beginning was to use the money for high-risk, high-payoff work with an emphasis on translation," said Hal Moses, M.D., the Center's director emeritus and director of the Preston Laboratories.

That investment has yielded high return. The Center's \$69 million in annual funding from the National Cancer Institute places Vanderbilt-Ingram among the top 10 cancer research centers in the country as measured by competitive NCI grant support.

Vanderbilt-Ingram's strategy also aligns nicely with Martell's vision to push boundaries "We fund eight very significant cancer centers, but Vanderbilt truly is a jewel in the crown," said Peter Quinn, CEO of the T.J. Martell Foundation. "We want to fund out-of-the-box thinking, things that haven't been tested before, and if we can get some traction with those findings, it's brilliant. Vanderbilt is exquisitely good at leveraging our money."

In the early days, the Preston Laboratories were among the first to explore the genetics of cancer. Today, the focus is on early

detection/prevention and proteomics (the study of proteins) to individualize diagnosis and treatment based on markers in blood and tissue. Funds from Martell have been used to jump-start several important initiatives, including the Southern Community Cohort Study, aimed at understanding why African-Americans and people in the Southeast are more likely to develop and die from cancer. Martell support has also recently yielded information about how the cells surrounding the tumor contribute to cancer's development and spread and the discovery of a way to "tag" tumors that are responding to therapy with a light-emitting molecule so doctors can gauge within days whether a treatment is working.

One of Preston's favorite photos shows Preston and Moses as equal partners in making the science happen. While it's not a wedding portrait, it is symbolic of a relationship that Preston often likens to "a perfect marriage."

"The artists and the scientists have come to respect each other so much, and the artists love Hal," Preston says. "When we realize that the money we raise enables cutting-edge research that we

Left to right: Hal Moses and Frances Williams Preston in the lab; Aaron Benward and Scott Reeves (of Blue Country) with Eddie Montgomery and Troy Gentry (of Montgomery Gentry) at the 14th annual Country in the Rockies in 2008; Richard Marx and Kenny Loggins entertain the audience at the 2007 Country in the Rockies.



JOHN HOWSER

## OTHER MARTELL-SUPPORTED CENTERS ARE LOCATED AT:

**Columbia-Presbyterian Cancer Center**

**Harvard/Massachusetts General Cancer Center**

**Memorial-Sloan Kettering Cancer Center**

**Oregon Health and Science University Children's Hospital Los Angeles**

**Mayo Clinic**

**Mt. Sinai Medical Center in New York**

might not have been able to do, it makes us really feel a part of it. That makes our marriage stay together.”

The Martell Foundation's fund-raising model brings fans and artists together “to have fun raising funds” at concerts, ski events, wine auctions, bowling and fishing tournaments and the like. Preston's idea for a ski-and-music event in her favorite Colorado resort, Crested Butte, quickly became the Nashville division's signature event called Country in the Rockies.

The gathering became a family reunion of sorts for a group of regular attendees, with Moses and Preston as the symbolic heads of the family. They have shared happy times, including marriages and the births of children, but also sad ones. Moses has taken phone calls from many music industry friends over the years, seeking advice about a cancer diagnosis of their own or a loved one. Artist Van Stephenson of Blackhawk missed one year's event to undergo surgery for melanoma, and later died of the disease; his bandmates began a memorial fund in his honor. Charlie Daniels and his manager, David Corlew, both became cancer survivors. And each time cancer struck so close to home, it only reinforced the music industry's commitment and the scientists' determination to end this disease.

Singer-songwriter Kathy Mattea, part of the line-up for the first Country in the Rockies and now a member of the Center's Board of Overseers, was among those who turned to “Dr. Hal” for help when her father developed cancer.

“Vanderbilt got my Dad into a study in Knoxville, Tenn., which prolonged his life for about six months,” she says. “But larger than

that, what they gave my Dad was an opportunity to add a layer of meaning to his struggle with cancer. He used to say, ‘maybe someone will be able to get this drug because of what they are learning from me right now.’ Shortly after he passed, that drug came on the market.”

Other artists say their motivation to become and stay involved is also personal.

“After losing my mother to cancer, what T.J. Martell and Vanderbilt do really hits close to home,” says Troy Gentry of Montgomery Gentry. “I see how hard everybody works and where the money goes and how it impacts the research ... It means a lot to me.”

After headlining Country in the Rockies last year, the country music duo has offered to host the newest in the Martell Foundation event line-up – Country on the Beach next winter in Cancun.

While it may be easier to point to the differences between the music and science fields, Quinn says there is an important similarity. “Music and medicine are always looking to the future,” he says. “In music, it's the next new sound. In science, it's the next big discovery.

“But we're always asking ‘what's next?’”

Martell and Vanderbilt will be asking – and answering – that question together. ☺



web link

More information about the T.J. Martell Foundation at: [www.tjmartellfoundation.org](http://www.tjmartellfoundation.org)



RANDI RADCLIFF



# recipe



FOR A HEALTHIER TENNESSEE

Coalition reaching out to  
loose cancer's grip



*By Dagny Stuart | Photography by Anne Rayner*







The TC4 childhood action team decided to create learning modules on several cancer topics – including nutrition – all aimed at young children in day care centers.



Faces bright and eyes shining, groups of 4- and 5- year-old preschoolers take turns dipping their fingers into bags of cereal, marshmallow and raisins, and furiously mixing the colorful concoction to create a scrumptious and nutritious trail mix.

These “cooking classes” at the Northside Baptist Church Preschool in Rutherford County, Tenn., – and at several other preschools and day cares throughout Middle Tennessee – are part of an effort to teach these youngsters about the link between healthy food and healthy living and to provide tools that may help them reduce their risk of cancer later in life.

The Day Care Centers of Excellence Program is the brainchild of members of the Tennessee Comprehensive Cancer Control Coalition (TC4), a statewide organization dedicated to reducing the burden of cancer in the state. The Coalition is an organization of more than 400 health care professionals, volunteers, scientists, cancer survivors, family members and anyone who is interested in the subject of cancer in Tennessee. In addition to the statewide

leadership structure, the Coalition is organized into five regional planning groups.

In Middle Tennessee, the Coalition wanted to target their message of prevention to young children.

“We asked how we could hit these kids with the prevention message when they are very young, not just about cancer but about all of these serious health issues,” said Cindy Chafin, project director and consultant for the Middle Tennessee State University Center for Health and Human Service and a member of the Coalition. In response to that question, the TC4 childhood action team decided to create learning modules on several cancer topics – including nutrition – all aimed at young children in day care centers.

“We used the book ‘The Very Hungry Caterpillar,’ a story that ties into nutrition, and we did a coloring activity related to the book,” Chafin explained. “We read stories about the food pyramid, sang songs and had some big displays from the ‘More Matters’ campaign to increase consumption of fruits and vegetables.

“In the past few months we have taken this curriculum to five day care centers in seven locations throughout the central part of the state. It’s a pilot program that we hope to expand.”

This day care education campaign is just one example of the outreach projects created and delivered by the TC4, a young organization whose members started meeting informally in 2001. By 2003, the Tennessee Department of Health received the first two-year planning grant from the federal Centers for Disease Control and Prevention. While small, the grant allowed TC4 members to do more than dream about how to attack cancer in Tennessee. It allowed them to develop a blueprint for change.

“At the end of the two years we had our first statewide cancer control plan ready to roll out into grassroots efforts,” said Debra Wujcik, R.N., Ph.D., co-chair of the TC4. She is also the director of Clinical Trials at Meharry Medical Center for Vanderbilt-Ingram Cancer Center and an associate professor in the Vanderbilt University School of Nursing.

Wujcik maintains there is much to do at the grassroots level if the Coalition wants to reduce cancer rates in the state. Tennessee sits squarely in the middle of the Southern Cancer Belt, a swath of states with a much higher incidence of cancer than the rest of the United States. Lung cancer is near the top of that list.



The TC4’s day care education campaign teaches children healthy habits that could help reduce their risk of cancer. Below, TC4 representative Cindy Chafin (right) shows Northside Baptist Church Preschool students Logan Chapman (left), and Anna Creel healthy food options. Previous page: Ellie Henry mixes up a healthy trail mix snack.





“Tennessee has major issues with tobacco use and obesity, and those two issues alone are responsible for most of the cancer and cardiac problems of patients,” Wujcik said. “If we could make changes in the way people eat, the amount of exercise they get and stop them from smoking, we would make a huge dent in the cancer problem in Tennessee.”

As part of this mission, the Coalition worked with other groups to promote the new statewide ban on smoking in most public places as well as the Tennessee Tobacco QuitLine, a telephone-based smoking cessation program. The programs appear to be working. Adult smoking rates in Tennessee dropped from 26.8 percent in 2005 to 22.6 percent in 2006, and QuitLine calls jumped from 700 a month in 2006 to 3,300 in October 2007.

Persuading Tennesseans to change their habits requires education and outreach to groups that may not have access to good health care information. That’s why Sheila Bates, LMSW, Vanderbilt-Ingram manager for Community Outreach, spends so much time traveling around the state with a message about cancer prevention.

“Regular exercise has been documented to reduce the risk of colorectal cancer by 40 percent, which is just amazing,” said Bates, who is the chair of the Colorectal Cancer Resource Group for the Coalition. “That’s one of the facts I use when I set up colorectal cancer bingo games at community centers.”

The bingo game – developed by the Vanderbilt-Ingram Office of Patient and Community Education – has been a big hit, Bates said. Each square of the bingo card contains facts about colorectal cancer risks, screening tests and how to reduce your risks.

“We read the facts aloud, the participants find them on the squares and mark them off, and at the end of the game everybody gets a prize,” she explained. Vanderbilt-Ingram donates funds for those prizes.

Bates also spreads the message about the importance of colorectal cancer screening.

“The amazing thing about colorectal cancer is it is preventable if you’re screened – especially if you get a colonoscopy – because if the physician finds a polyp, the polyp can be removed before it becomes cancer. It’s so exciting when you work in oncology to have a good message to give to people,” Bates said with a smile.

Bates encourages TC4 members in each region of the state to share their outreach experiences.

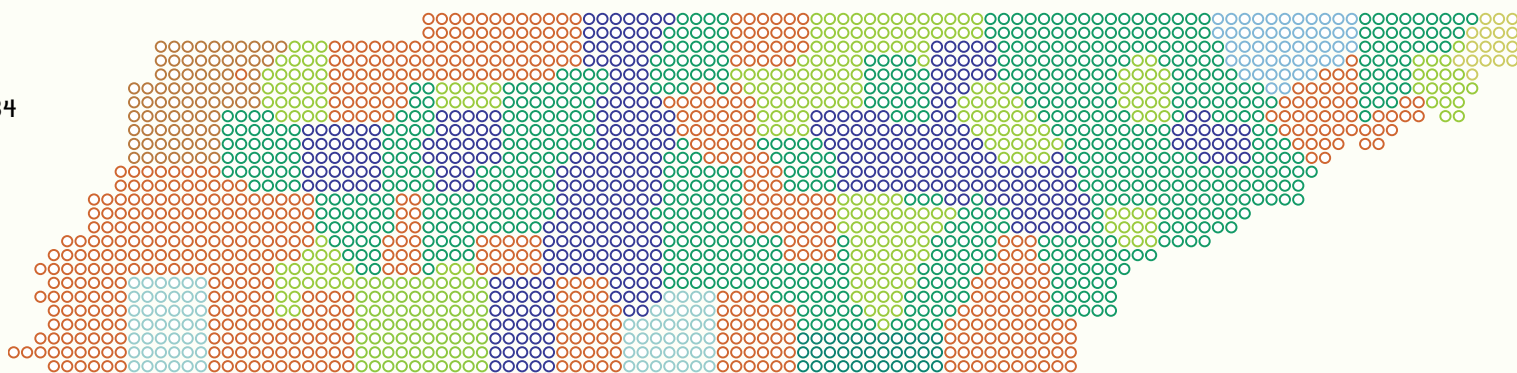
“If a program in East Tennessee went well, we want them to tell us what worked, what didn’t and how they publicized the event so we can share best practices.”

At the statewide level TC4 has logged a number of successful initiatives. In partnership with the Tennessee Breast and Cervical Cancer Early Detection Program, TC4 established the Witness Project of Davidson County which employs breast and cervical cancer survivors to “witness” to African-American women about the importance of cancer screening. TC4 recruited participants for the national Sister Breast Cancer Study, including many African-American women who may be at high risk for an aggressive form of breast cancer.



The Cancer Queens take their message of cancer prevention to the stage at Ladies Night Out: Protecting Yourself Against Cancer in October 2008. The “edu-tainment” musical presented by Vanderbilt-Ingram’s Office of Patient and Community Education features Sheila Bates, Cindy Chafin and six other TC4 representatives.





In a project led by Jacob Weiss, a doctoral student at Vanderbilt University, the TC4 worked with other Middle Tennessee cancer hospitals, survivors and nonprofits to establish CanConnect (<http://canconnect.org>), a free interactive Web site that makes it easy for

cancer survivors and providers to connect online.

Coalition members are also bringing their message of cancer prevention to the stage with “Cancer Queens! A Cancer Prevention Musical Revue,” an “edu-tainment” musical presented by Vanderbilt-Ingram’s Office of Patient and Community Education. The queens – including Bates, Chafin and six other TC4 representatives – debuted at Vanderbilt in October 2008 and have scheduled performances across the state in 2009.

Despite all of these initiatives and messages about prevention, far too many Tennesseans continue to develop cancer, which is why the TC4 includes the concept of control.

“Cancer control is a very odd term, but when we think about control, we’re talking about everything that happens to the patient from the time they have a positive screening test,” said Debra Friedman, M.D., leader of the Vanderbilt-Ingram Cancer Control and Prevention Program and director of the Cancer Survivorship program.

“Cancer control includes the original diagnosis, what kind of care the patient was offered, whether they were offered access to a clinical trial, and whether they had options about where to receive their care,” Friedman explained. “Once treatment is started, cancer control includes pain and symptom management and health-related quality of life. For those who are successfully treated, control

includes navigating long-term survivorship to remain healthy, and for those who ultimately cannot be cured, it includes palliative care.”

However, access to treatment, to clinical trials and to services like palliative care may not be available in every part of the state. And each county’s cancer burden may be different. The state’s Tumor Registry, which recently achieved Gold Status from the North American Association of Central Cancer Registries, has complete data on cancer incidence by county, which allows TC4 to develop regional reports so members can focus their efforts on the needs in their part of the state.

But the biggest barrier to better cancer screening and prevention services may be money. And it starts with a lack of insurance coverage.

“We are meeting with Blue Cross/Blue Shield of Tennessee and the American Cancer Society to introduce legislation that would require health insurers to pay for colorectal cancer screening,” said Wujcik. “We’re not just telling the insurance companies to do this, we’re trying to figure out how to do it, what makes sense and what is affordable for the state and for the insurers.”

While TC4 has already achieved several milestones, Wujcik has additional dreams for the future of the Coalition.

“I want us to have a line item in the state budget so that we are well-funded and are not worried about funding the structure of the organization,” she said. “I would love to see us be able to facilitate research that is specific to the cancer issues in Tennessee.”

When it comes to cancer, Wujcik believes it’s important to dream big. ☺

“If we could make changes in the way people eat, the amount of exercise they get and stop them from smoking, we would make a huge dent in the cancer problem in Tennessee.”

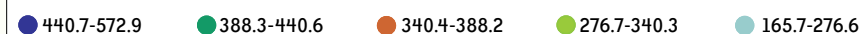


– Debra Wujcik, R.N., Ph.D., co-chair of TC4



## Cancer Incidence Rate in Tennessee

by county, per 100,000 people



Developed by the Office of Cancer Surveillance in support of the Tennessee Comprehensive Cancer Control Coalition (TCCCC)

December 2007

# Outreach across the map

The Tennessee Comprehensive Cancer Control Coalition (TC4) is able to accomplish its goals through generous support from member organizations, including in-kind contributions and time commitments from health care executives like Anne Washburn, MPH, associate director of the Office of Patient and Community Education at Vanderbilt-Ingram Cancer Center.

"The beauty of the Coalition is that when people from all of these health care, advocacy, government and nonprofit groups come together we can leverage our resources," Washburn said. "We each spend time on cancer projects in our daily 8-to-5 jobs, but when we come to the Coalition we're taking off our daily hats and coming together as a group of citizens who want to do good things for all of the citizens of our state by reducing the burden of cancer."

That includes outreach and education for all Tennessee citizens.

"We are wonderfully fortunate in this country to have resources like the National Institutes of Health, the National Cancer Institute, and the Centers for Disease Control and Prevention," said Washburn. "They're developing wonderful information about health care, but until we actually take it out to our communities and disseminate that information, it's not worth much."

As a National Cancer Institute-designated Comprehensive Cancer Center, Vanderbilt-Ingram Cancer Center has a special mission to provide educational outreach. While many health care organizations may call themselves "comprehensive," NCI designation requires more than state-of-the-art cancer care and services. It also includes a strong research base as well as a wide spectrum of activities to support cancer education and prevention. Vanderbilt-Ingram is one of just two Comprehensive Cancer Centers in Tennessee and 40 in the nation. A strong history of community outreach is one of the reasons for that recognition.

"We focus on being creative in our outreach and mindful of the different populations we're trying to reach," Washburn explained. "We have to think about minorities, the underserved, low literacy rates in some areas, and how people learn when we're trying to give them relevant health care information. We also recognize that there are enormous disparities in the availability of resources across the state."

From Memphis to Mountain City, TC4 members are identifying those disparities and trying to fill in the gaps so they can help all Tennesseans.

Washburn is the TC4 state chair for the Cancer Care committee, a group of profes-

sionals with expertise in the continuum of cancer care, quality of life, palliative care and survivorship issues.

"Our committee has recognized that, for patients and families, there is a lack of resources focusing on end-of-life issues, and those resources vary dramatically from one county to the next," Washburn said. "So we have done an assessment of each county in the state to determine what palliative care and end-of-life resources exist, and we've put together a database. We're working with members in each region of the state to determine the best way to implement that database to ensure that patients, caregivers and health professionals know about these resources in their area."

Washburn says the Coalition recognizes that each region of the state is quite different, with varying populations, cancer incidence, and mortality rates.

"It is gratifying that we all see the big cancer picture and the demanding issues related to cancer prevention, and we're able to divide up and tackle specific issues for the benefit of all of our citizens."



web link

More information about the TC4 at:  
<http://health.state.tn.us/cccp/index.htm>



## STORIES OF SURVIVAL

STEPHANIE CROWE

In Her Own Words

“Life is not measured by the number of breaths we take, but by the moments that take our breath away.”

– Anonymous

Since the age of 8, I've had many moments that have taken my breath away – some wonderful, and some petrifying.

For most 8-year-olds, their biggest worries are having to go to school every day and summer flying by much too quickly. When I was 8 years old, I had my first colonoscopy. It was the first in a long line of procedures, tests and surgeries I've had to fend off the looming threat of colon cancer.

My biological father had familial adenomatous polyposis (FAP) – a hereditary condition that causes numerous polyps in the colon and rectum. If not treated, nearly all FAP patients will go on to develop colon cancer. When he was in his early 20s, my father had surgery to remove part of his colon. He didn't stay on top of his follow-up care, and around the age of 35 he was diagnosed with colon cancer.

By age 8, I was already showing some symptoms of FAP (passing blood and slight bowel changes), so my mother set up the appointment for my first scope.

Thirty-five years ago, hospitals were not as child-friendly as they are today. I didn't understand why the nurse and doctor were doing such hurtful things to me. I remember hearing the doctor apologize to my mother about having to use a rigid proctoscope. It was the only one they had; there were no pediatric-sized scopes.

The doctor saw what he described as little hobnails in my colon. While the polyps were very small, my colon was carpeted with them. The doctor recommended that I be monitored because he felt I was too young for surgery at that time.

Countless hospitals, scopes and opinions later, I was officially diagnosed with FAP at age 12. And just before I turned 15, my entire colon was removed.

I recovered very quickly after my surgery. When you are young, it is amazing how fast you bounce back. Other than my new “battle scar” and my biannual scopes, I was a normal teenager. No one would guess that I had had my colon removed. It didn't slow me down.



By Stephanie Crowe | Photograph by Dana Johnson







(Left to right): Stephanie, age 8, when her battle with FAP began; Stephanie and son Zach at age 8; Stephanie, at a recent clinic visit, is evaluated by Alice Nash, R.N.



DANA JOHNSON

I now realize that we had no idea what having FAP truly meant and no idea what was to come. As far as we knew, we had done the hard part with my colectomy. Now it was just a matter of the inconvenience of my scopes to check my rectum for polyps. It was just two days out of every year. That didn't sound so bad. Little did we know what was in the future.

At age 21, I got married, and five years later, Bennie and I were blessed with our beautiful baby boy, Zach, who was delivered by Caesarean section. We were so excited to be parents.

But not long after my C-section, I noticed that my scar didn't look quite right – a lump had formed in my scar line. My OB/GYN thought that it was just scar tissue and that we could handle that in the future when I had another child. But after two-and-a-half years I finally put my foot down. I knew that something was wrong.

I'll never forget the day I received the call from the general surgeon to tell me that I had Gardner's Syndrome. I quickly told him that he was mistaken, that I had FAP. He told me about Gardner's Syndrome – that it was a variant of FAP, and in addition to forming polyps in my colon, I could (and had) formed tumors in my abdomen. The abdominal tumors I had were "desmoid" tumors, which are benign and locally invasive but do not metastasize. Even

though these tumors don't metastasize, the destruction they can cause to vital organs can be life-threatening.

I thought I had known what FAP was – just polyps in my long-gone colon and now occasional polyps in my rectum. Not a huge deal, or so I thought. Now I was finding out that it was a much bigger deal.

I felt like my world had been turned completely upside down. Learning what this disease truly was brought me heartache because we had a small, precious toddler by now. Every time someone would tell me how much he looked like me, I would say a silent prayer that looking alike was where it stopped. I remember praying that I would take any surgery I had to if my baby could be OK and never have to go through this.

I was told that because of the risk of passing this on to future children, my danger of developing more desmoids, and my inability to be able to carry another baby to term after my abdominal reconstruction, that it would be best to have my tubes tied. For Bennie and me, there was no decision to be made. We knew that the doctors were right. So in 1994, during a surgery to remove the desmoid tumors, I had a tubal ligation. But it was still a sad time for me because I was a young woman (29 years old) giving up my ability to have children.



I continued to battle the desmoid tumors. For a while, I felt good and life went on. During that time, my husband and I decided to have the genetic testing on Zach and myself.

Waiting on the results was very hard. We wanted to know, but we were scared what we would find out.

The most wonderful part of this whole story is that our son does not have FAP. The doctors were able to identify the defect in my APC gene that caused my disease. Zach's APC gene doesn't have the defect; therefore, in my family, FAP stops with me!

While I'm thankful that my son will not have to face this disease, my battle continues.

In 2001, I began having more trouble with polyps in my rectum. The week before my son's 10th birthday, I had to have multiple biopsies. Later that week I was really struggling, not feeling well, and passing blood.

But as a mom, I didn't have time to not feel well. The morning of Zach's birthday party, I passed out and hemorrhaged on our bathroom floor. I remember hearing Zach laughing and jumping on my bed, excited about his basketball game and birthday party later that afternoon. When I came to, the floor was covered in blood. I was scared, but I knew that I had to stay focused and awake. I was having a hard time staying awake, and I was too weak to even walk. I didn't know if I was going to make it.

We found out at the hospital I had lost over five units of blood. While I was in the hospital, my mother spoke to a friend of hers that had connections with Vanderbilt. She wanted to know who I should see there. As my mother, she wanted what was best for her "baby" – just as I now want what's best for my "baby."

Vanderbilt soon became what I teasingly call my "second home." I have been blessed with a team of doctors that truly care about me as a person, not just a "science project." I have been to a lot of teaching hospitals in my life, and some of them have made me feel like I was their show-and-tell science project. Vanderbilt has never made me feel that way.

I have had way too many surgeries, procedures and treatments to count. These days if I am asked on a form to list any previous surgeries, I laugh to myself and write on the form "not enough space to list."

Right now I am living with multiple inoperable desmoids in my abdomen. One is wrapped around my right ureter; another one has a couple loops of my small bowel entangled in it.

For the past two years, I have had an open wound, and with the approval of my doctors, I've postponed surgery to repair it. After all the years of living with drains, being on intravenous nutrition and not being able to eat during a lot of those years, so many surgeries, and way too much other stuff, I can handle taking care of an open wound.

I have a choice for now to just enjoy my life, even the simplest things, like being able to eat. For most people eating is just something you do multiple times every day; to me eating is one of life's little pleasures. And down the road I will tackle that next big surgery.

## FAP FAQs

### What is FAP?

Familial adenomatous polyposis (FAP) is an inherited condition in which numerous benign growths, or polyps, form mainly in the inner lining of the large intestine (the colon and rectum). If the colon is not removed, these polyps almost always become malignant by the age of 40.

### What are the symptoms of FAP?

Beginning in early adolescence, patients with FAP develop hundreds to thousands of polyps. These may cause blood in the stool, anemia (low blood counts) due to blood loss, weight loss and/or altered bowel habits.

### What causes FAP?

There are two main genetic defects responsible for FAP.

The most common form of the disease is caused by a mutation in the *APC* (adenomatous polyposis coli) gene. *APC* normally acts as a "tumor suppressor" that limits unchecked cell growth. Except for sperm and eggs, every cell in our bodies has two copies of the gene – one inherited from each parent. You only have to inherit one copy of the mutant *APC* gene to have the disease, meaning this mutation is "autosomal dominant."

FAP can also be caused by mutations in another gene, called *MUTYH* (MYH glycosylase). The gene encodes a protein that repairs DNA damage that happens during normal cellular activities. Mutations in the *MUTYH* gene are inherited in an "autosomal recessive" pattern, which means two copies of the gene must be altered for a person to be affected by the disorder.

### How common is FAP?

FAP is rare, accounting for only about 1 percent of colorectal cancer cases. Estimates range from 1 in 7,000 to 1 in 22,000.

### How do I find out if I have FAP?

It is important to know your family history, i.e., if a close family member has had FAP or colon cancer. There are now several blood tests that can tell you if you have inherited one of the mutations that cause FAP. If FAP is suspected based on your symptoms or genetic background, a colonoscopy or other colon imaging studies should be done to look for polyps or tumors.

### How is FAP treated?

To prevent colon cancer from developing, the colon must be surgically removed by a procedure called a colectomy. Certain drugs (e.g., celecoxib and sulindac) may also be used following surgery to reduce the number and size of polyps in the rectum. After the colon is removed, regular screenings to check for polyp recurrence in the rectum are required.



Despite the pain, worry and “hassle” of dealing with this condition,  
I am happy to be here. God didn’t make a mistake on me.  
I am exactly who I am supposed to be.

Over the last few years I have shared my experiences and support with newly diagnosed patients. Recently I have been blessed with the privilege of being a part of the patient advocates at Vanderbilt and have had the opportunity to speak to first-year medical students about my case history and genetics. My hope is that through my story and my experiences, I can help patients, physicians and researchers better understand and deal with this disease. I have always felt that if I can help at least one person, then everything I have been through is more than worth it.

The fellow survivors and family members I have met through this program have inspired me with their strength and dedication. I am honored to be a part of this wonderful group of people and to help spread the word about proper screening – not only for people with family histories or genetic predisposition to cancer, but everybody.

Colonoscopies and genetic screening may sound scary. But, when I speak about the importance of these life-saving measures, I use my story of being a tiny 8-year-old little girl having my first scope. I tell them that if a little 8-year-old girl can handle it, then surely they can.

Despite the pain, worry and “hassle” of dealing with this condition, I am happy to be here. God didn’t make a mistake on me. I am exactly who I am supposed to be.

Those many “moments that have taken my breath away” – both the joyous ones and the heart-wrenching ones – are all together a part of who I am today. My hope and prayer is to make a difference, love deeply, and to enjoy every moment I am here. In my eyes that is a life well lived. ☺

Stephanie enjoys a day at the park with son Zach, husband Bennie, and their new puppy, Buddy.



DANA JOHNSON





SUSAN URMY

## Cancer Center opens new outpatient space

On Sept. 1, 2008, the Henry Joyce Cancer Clinic moved to the first floor of the Vanderbilt-Ingram Cancer Center, completing a yearlong construction project to double capacity for outpatient cancer care.

Patients and visitors now see a vastly different registration area with staff at six welcome stations helping patients check in for their appointments. A spacious new waiting area, larger public restrooms and better navigation signage are designed to make visits easier and more comfortable for patients and family members.

The new clinic space also is designed to create less confusion as patients move from initial lab areas to examination rooms. There are sub-waiting rooms next to internal clinics where family members or visitors can wait for patients.

The expanded clinic area offers more than cosmetic enhancements. Treatment rooms feature the same kind of lighting found in operating rooms, to make it easier for medical staff to perform sensitive activities like removal of a central line or for gynecologic procedures like colposcopies of the cervix. There are also procedure rooms available for gastrointestinal cancer experts to do scopes of patients' digestive tracts.

The newly designed space also includes a laboratory, which should speed the process of getting lab results.



SUSAN URMY

The expanded registration area (top) and on-site laboratory (bottom) are just two features of the recently renovated clinic space.

This isn't the last phase of the expansion. Later this spring, the chemotherapy infusion area will move up to the second floor of the Cancer Center, with 45 infusion beds, nearly double the current number of beds.

Fundraising for the project continues, with more than 500 donors contributing to the \$10 million campaign.

— by Dagny Stuart

## Bates lands public health educator award

Sheila Bates, manager of Community Outreach for Vanderbilt-Ingram Cancer Center, has been named the 2008 Health Educator of the Year by the Tennessee Public Health Association.



The award is given annually to an individual who displays a true passion for helping patients and the public understand the benefits of disease prevention and the latest in treatment advances.

Bates is responsible for developing programs on cancer prevention and early detection that are both educational and entertaining. She serves as the Colorectal Cancer Resource Committee Chair for the Tennessee Comprehensive Cancer Control Coalition and also has implemented a pilot program providing life coaching to cancer survivors.

— by Dagny Stuart

## Cancer Center Team Grows

The Vanderbilt-Ingram Cancer Center team of researchers, physician-scientists and clinicians continues to grow. Faculty who joined Vanderbilt-Ingram in 2008 include:

Deborah Friedman, M.D., E. Bronson Ingram Chair in Pediatric Oncology

Jonathan C. Nesbitt, M.D., associate professor of Thoracic Surgery

Eric L. Grogan, M.D., M.P.H., assistant professor of Thoracic Surgery

Vicki L. Keedy, M.D., assistant professor of Medicine (hematology/oncology)

Stephen A. Strickland Jr., M.D., assistant professor of Medicine (hematology/oncology)

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

J. Michael Thomson, Ph.D., assistant professor of Cancer Biology

Liana Desharnais Castel, Ph.D., MSPH, assistant professor of Medicine

Dineo Khabele, M.D., assistant professor of Obstetrics and Gynecology





### Price right to fill CEO role at Cancer Center

Beth Price, MBA, has been named to the newly created position of chief executive officer of the Vanderbilt-Ingram Cancer Center.

Price has served as oncology operations strategist for Vanderbilt-Ingram and Vanderbilt Medical Group since June 2007, where she assisted in the development and implementation of the regional market oncology strategy and served as interim business officer for the Cancer Center.

As CEO, Price will be responsible for expanding quality cancer services in the Middle Tennessee market and the Southeast, enhancing Vanderbilt-Ingram's status as a top 15 National Cancer Institute-designated Comprehensive Cancer Center

and providing administrative and business leadership.

"Beth Price has been an invaluable addition to our Cancer Center enterprise," said Jennifer Pietenpol, Ph.D., director of Vanderbilt-Ingram. "She has a tremendous ability to articulate a vision, develop strategic plans and execute those plans."

"As we expand our clinical services locally and regionally, we will rely on Beth's management skills and expertise to help us offer the highest quality health care to treat cancer patients as well as develop prevention programs and long-term follow-up care for cancer survivors."

A native of Rochester, N.Y., Price earned her Bachelor of Science degree in Health Information Management from Ithaca College, N.Y., and her MBA from Suffolk University, Boston. She has served as senior manager for strategy and business

architecture for Accenture and in management positions at Partners Health Care System, Massachusetts General Hospital and Roger Williams Medical Center, affiliated with Boston University School of Medicine. Before joining Vanderbilt-Ingram, Price was chief operating officer for Sarah Cannon Research Institute in Nashville.

"I am delighted by the opportunity to help lead the extraordinary team of professionals at Vanderbilt-Ingram Cancer Center," Price said.

"I am impressed daily with the level of talent, commitment and compassion for patients exhibited by physicians, researchers and staff at the Cancer Center and I am looking forward to working with them to expand and refine our services to those patients and our community."

— by Dagny Stuart

Availability of programs like these group exercise classes at HealthPlus were an important factor in the Cancer Center's CEO Cancer Gold Standard™ accreditation.

### Vanderbilt-Ingram recognized for cancer care efforts

Vanderbilt-Ingram Cancer Center has been accredited with the CEO Cancer Gold Standard™ certification recognizing the center's commitment to the health of employees and family members by certifying its efforts to meet a high standard of cancer prevention, screening and care guidelines.

To earn CEO Cancer Gold Standard™ accreditation, an organization must establish programs to reduce cancer risk by discouraging tobacco use, encouraging physical activity, promoting a healthy diet, detecting cancer at its earliest stages and providing access to quality care, including the availability of clinical trials.

In addition to sharing information with employees about healthy lifestyle choices, Vanderbilt University Medical Center provides a free fitness center for employees. The Cancer Center also operates the Cancer



Information Program, featuring a toll-free hotline staffed by oncology nurses who address questions about cancer treatment options and clinical trials at the Cancer Center. The nurses can be reached at (800) 811-8480.

The CEO Cancer Gold Standard™ was created by the CEO Roundtable on Cancer —

a nonprofit organization of cancer-fighting CEOs — in collaboration with the National Cancer Institute, many of its designated cancer centers, the American Cancer Society, the Centers for Disease Control and Prevention and leading health professionals.

— by Dagny Stuart

## Cancer “team science” efforts get boost

Vanderbilt-Ingram Cancer Center’s Specialized Programs of Research Excellence (SPOREs) in breast cancer, lung cancer and gastrointestinal cancer were recently renewed by the National Cancer Institute. The NCI established organ-specific SPOREs in 1992 to promote interdisciplinary research with a “translational” emphasis that spans the gap from basic science discovery to clinical application.

VICC is one of only seven centers to hold three or more SPORE grants.

### BREAST SPORE

Vanderbilt-Ingram’s SPORE in Breast Cancer – first funded in 2002 – was renewed in 2008, providing \$12 million over five years. Carlos Arteaga, M.D., is program director and Jennifer Pietenpol, Ph.D., is co-director.

The grant supports four research projects led by: Arteaga; Pietenpol; Ingrid Mayer, M.D.; Gregory Mundy, M.D.; Jeffrey Smith, M.D., Ph.D.; and William Dupont, Ph.D.

### LUNG SPORE

In 2007, Vanderbilt-Ingram’s SPORE in Lung Cancer received a renewal of \$11.5 million over five years. It is one of only six lung cancer SPOREs in the country and is directed by David Carbone, M.D., Ph.D.

Project leaders for the grant’s five research projects are: Carbone; Pierre Massion, M.D.; Daniel Liebler, Ph.D.; Yu Shyr, Ph.D.; David Johnson, M.D.; Richard Breyer, Ph.D.; Joe Amann, Ph.D.; Thao Dang, M.D.; Pran Datta, Ph.D.; Harold Moses, M.D.; Alan Sandler, M.D.; Quiyin Cai, Ph.D.; and William Blot, Ph.D.

### GI SPORE

Also in 2007, Vanderbilt-Ingram’s SPORE in Gastrointestinal Cancer – one of only five such programs in the country – was renewed, providing \$11.8 million over five years. Robert Coffey, M.D., is the program director.

The GI SPORE supports four research projects led by: Coffey; Jordan Berlin, M.D.; Daniel Beauchamp, M.D.; Ethan Lee, M.D., Ph.D.; Albert Reynolds, Ph.D.; Mary Kay Washington, M.D., Ph.D.; Reid Ness, M.D., M.P.H.; and Wei Zheng, M.D., Ph.D., M.P.H.

– by Melissa Marino



## Sosman lands award from American Cancer Society

Jeffrey Sosman, M.D., professor of Medicine, has received the first American Cancer

Society Mary Hendrickson-Johnson Melanoma Professorship.

The \$400,000 award, which runs through the end of 2013, is given to an outstanding investigator who has made a seminal contribution that has changed the direction of cancer research and who continues to provide leadership in the field of melanoma research. The award is based on a generous gift from the Mary Hendrickson-Johnson Foundation, named for Mary Hendrickson, who died from metastatic melanoma nearly 20 years ago.

Malignant melanoma is the most deadly form of skin cancer, accounting for

almost 4 percent of cancers among men and women. The incidence of melanoma has increased significantly for both men and women in the United States in the last 10 years. While both hereditary and environmental risk factors have been identified in melanoma, the critical molecular events in disease onset and progression remain unknown.

Sosman – the Ingram Professor of Cancer Research and Medicine and co-leader of the Signal Transduction and Cell Proliferation Program for Vanderbilt-Ingram – will continue his work in the development of new drugs and targets in the therapy of melanoma through clinical trials designed to benefit patients while asking important biologic questions.

– by Dagny Stuart



web link

Get more news about Vanderbilt-Ingram by visiting [www.vicc.org/news](http://www.vicc.org/news) and subscribing to our RSS feed.

Robb Kerr



## Vanderbilt-Ingram mourns longtime patient advocate

Robb Kerr, a dedicated Vanderbilt-Ingram patient advocate, died at his home in Nashville on Sept. 29, 2008. He was 43.

Soon after his diagnosis of advanced (stage IV) colorectal cancer in 2002, Robb became involved in clinical trials at the Cancer Center, participating in five clinical trials during his six-year battle. Robb became a patient advocate, sharing his clinical trials experiences with other patients.

Through his experience, Robb also became a passionate supporter of cancer research and was one of the first individuals to become a research advocate for the gastrointestinal cancer SPORE (Specialized Program of Research Excellence). As a research advocate, Robb participated in the design and oversight of cancer research, helped design patient consent forms, and shared his insights from participating in clinical trials with researchers.

Robb gave of himself tirelessly, reaching out to other patients informally in the clinic to share his experiences and support them in their journey. He also spoke out for the needs of Tennesseans without insurance and those who lost TennCare, working with advocacy organizations for change.

“Robb’s legacy to cancer research and patient advocacy will long be remembered and his spirit will live on in the hearts of all who were touched by him,” said Jane Kennedy, MSSW, manager of Patient Advocacy in the Office of Patient and Community Education at Vanderbilt-Ingram.

– by Melissa Marino



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

### Cancer drug allergy clues

Cancer patients in the Southeast are far more likely to suffer severe allergic reactions to the drug cetuximab (Erbix) – a monoclonal antibody approved for use in colon cancer and squamous-cell head and neck cancer – than patients in other regions of the country. In the *New England Journal of Medicine*, Christine Chung, M.D., and colleagues report that a pre-existing antibody – that reacts to sugar molecules added to the drug during its production – triggers the life-threatening allergic reaction. Based on the findings, a commercial assay to test patients for the troubling antibody before drug treatment is being developed. Chung and colleagues are continuing to search for the antigen that triggers the formation of these antibodies in Southerners.

### Rigid surrounds spawn aggressive cancers

Alissa Weaver, M.D., Ph.D., and colleagues have found a cellular explanation for why denser breast tissue is correlated with more aggressive tumors and a poorer prognosis. In *Current Biology*, they report that dense, rigid surroundings cause cancer cells to build more drilling structures – called invadopodia – with which to bore into the matrix around them. Breast cancer cells cultured on a denser, more rigid matrix had a greater number of active invadopodia than breast cancer cells cultured on a less dense matrix, they found. Two signaling proteins – FAK and p130Cas – were present in an activated state in the invadopodia, suggesting that they are important players in this response and possible targets for anti-invasive therapies.

### Good, bad sides of anti-cancer agents

Compounds known as “HDAC inhibitors” are currently being tested as anti-cancer agents in clinical trials, but how they execute their cancer-killing effects is unclear. In *Molecular Cell*, Scott Hiebert, Ph.D., and colleagues report that cells from mice lacking the HDAC3 enzyme die because they can't repair the DNA damage that occurs naturally when cells copy their DNA during cell division. This explains why HDAC inhibitors specifically kill rapidly dividing tumor cells while sparing healthy cells. Therefore, giving an HDAC inhibitor before chemotherapy or radiation may keep tumor cells from repairing the DNA damage inflicted by those treatments, they suggest. In a second study in the *EMBO Journal*, the researchers reported that mice lacking HDAC3 in the liver only developed extensive liver damage, developed grossly enlarged and fatty livers, and had major metabolic abnormalities. The studies provide a potential mechanism by which HDAC inhibitors specifically damage cancer cells and offer clues about possible adverse effects of these compounds.

### Halting cancer's wandering ways

It might be possible to stop metastasis by making cancer cells “stick” to the primary tumor. In *Cancer Cell*, Andries Zijlstra, Ph.D., and colleagues report that an antibody targeted to the CD151 protein prevents cancer cells from leaving the original tumor and blocks metastasis. CD151 associates with integrins – cell surface proteins responsible for adhesion to the matrix – and is expressed in a variety of human tumors. Using intravital imaging, the researchers found that tumor cells in antibody-treated chick embryos could move around a fixed point, but could not detach from that point and move away from the tumor. The antibody treatment prevented metastasis of two types of aggressive human cancer cells, epidermoid carcinoma and fibrosarcoma, suggesting that the immobilizing machinery may be common to different cancers.

### Security team for the genome

Genome “surveillance systems” prevent and repair DNA damage to maintain the genome's stability and protect against cancer-causing mutations. One such system in human cells includes a pair of proteins, ATR and ATRIP. In *Genes & Development*, David Cortez, Ph.D., and colleagues provide insight into how ATR-ATRIP complexes are activated by DNA damage. They found that another protein, TopBP1, activates ATR by interacting with surfaces on both ATR and ATRIP proteins. These interactions are required for cell survival and for restarting DNA synthesis after slowed or stalled DNA replication. The investigators also determined that related genome-maintaining enzymes share this mechanism of ATR regulation. The results provide a starting point for designing agents to disrupt genome surveillance systems and sensitize cancer cells to many chemotherapy drugs.

### Too many chromosomes spark tumors

Polyplody – having extra sets of chromosomes – may contribute to cancer development by promoting genomic instability, but it is unclear whether this instability drives tumorigenesis or is a consequence of it. Meejeon Roh, Ph.D., Sarki Abdulkadir, M.D., Ph.D., and colleagues report in *PLoS ONE* that polyplody causes genomic instability and has a direct role in tumor development in human cells. They expressed Pim-1, an oncogene implicated in the development of various tumors, in human prostate and breast epithelial cells. Pim-1 expression caused the gradual emergence of polyplody, allowing the investigators to sort the cells into diploid (normal chromosomal content) and polyplody populations. The polyplody cells were tumorigenic *in vitro* and *in vivo* and showed chromosomal abnormalities. The findings suggest that polyplody cells in human tumors may be attractive targets for novel therapeutics.



web link

More information about our research at:  
[www.vicc.org/research](http://www.vicc.org/research)

## New views of cancer

The Vanderbilt University Institute of Imaging Science (VUIIS) and Vanderbilt-Ingram Cancer Center recently received two major grants from the National Cancer Institute (NCI) to support cancer imaging research.

In 2008, the NCI awarded \$7.5 million for the establishment of the Vanderbilt “*In Vivo* Cellular and Molecular Imaging Center” (ICMIC). Research supported by the grant will focus on developing sensitive new imaging probes and assessing how specific *in vivo* molecular signal transduction pathways and changes in these pathways are modified by cancer and cancer therapy. A special focus of the program will be to develop innovative imaging biomarkers that can be used to predict and measure whether patients respond to specific treatments.

VUIIS and Vanderbilt-Ingram also received a five-year, \$2.2 million grant to apply new non-invasive imaging techniques for studying cancer in small laboratory animals. The funding helps establish the “South-Eastern Center for Imaging Animal Models of Cancer.” Vanderbilt will collaborate with 12 other centers in the NCI’s Small Animal Imaging Resource Program.

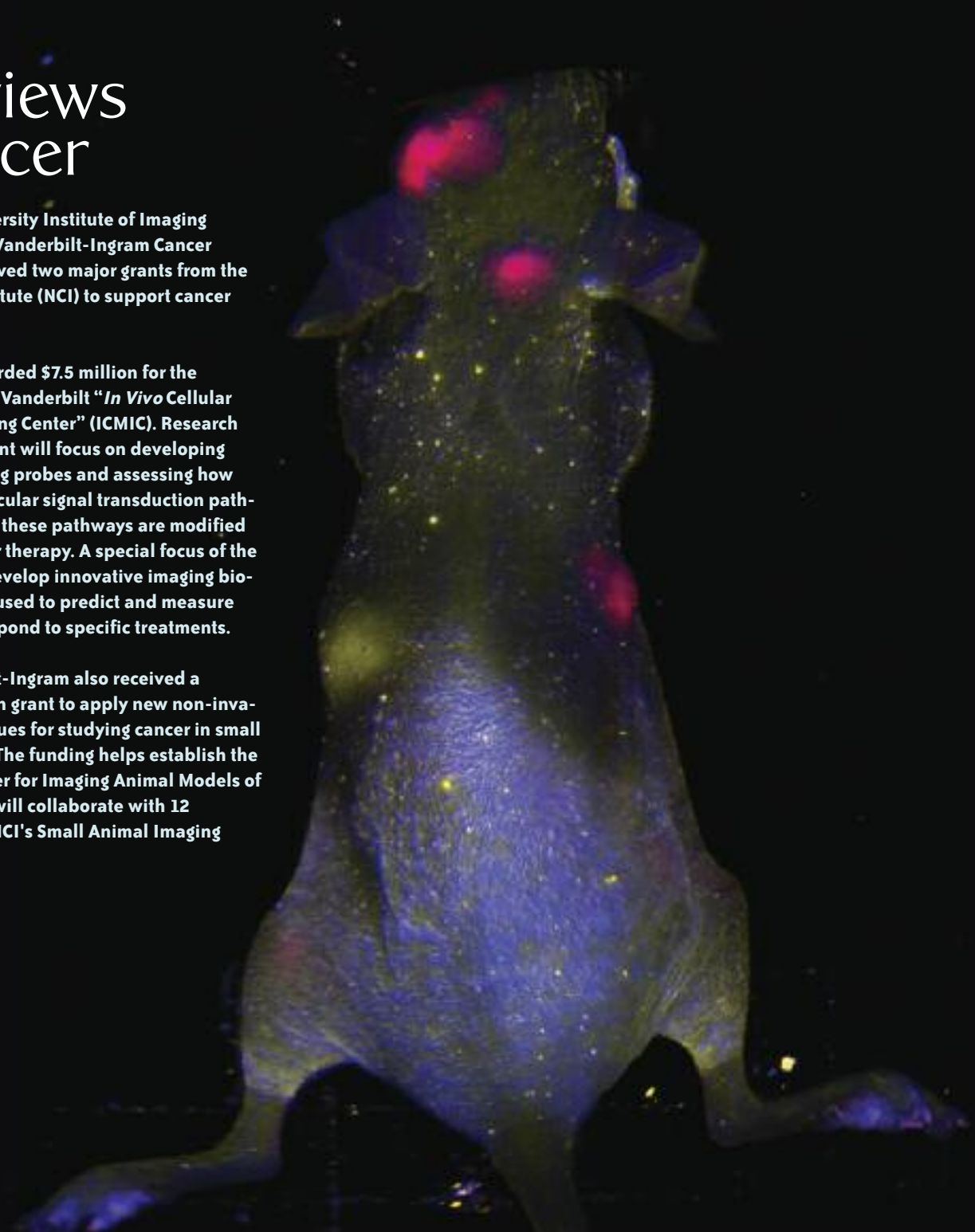


PHOTO: MULTISPECTRAL FLUORESCENCE IMAGING IN MICE HELPS INVESTIGATORS STUDY HOW BREAST CANCER CELLS (RED) METASTASIZE TO BONE. IMAGE PROVIDED BY H. CHARLES MANNING, PH.D., VUIIS





## Recipe for Health

The Tennessee Comprehensive Cancer Control Coalition is reaching out to teach all ages about healthy living and cancer prevention.

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